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Treatment With Protease Inhibitor and Development of Diabetes Among Medicare Beneficiaries With Human Immune Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS)

Eric Ejike Chinaeke

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TREATMENT WITH PROTEASE INHIBITOR AND DEVELOPMENT OF
DIABETES AMONG MEDICARE BENEFICIARIES WITH HUMAN IMMUNE
VIRUS/ACQUIRED IMMUNE DEFICIENCY SYNDROME (HIV/AIDS)

By

Eric Ejike Chinaeke

Bachelor of Pharmacy
University of Nigeria, 2008

Master of Pharmacy
University of Nigeria, 2012

Master of Global Public Health and Policy
Queen Mary University of London, 2013

Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Philosophy in

Pharmaceutical Sciences

College of Pharmacy

University of South Carolina

2020

Accepted by:

Kevin Lu, Major Professor

Brandon Bookstaver, Committee Member

Bryan Love, Committee Member

Gene Reeder, Committee Member

Minghui Li, Committee Member

Xiaoming Li, Committee Member

Cheryl L. Addy, Vice Provost and Dean of Graduate Studies

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DEDICATION

This dissertation is dedicated to my parents, siblings, and my wife for their support throughout the years of my PhD training.

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I am delighted to acknowledge the wonderful support and mentorship I received from many people without whose support this dissertation could not have been completed.

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ABSTRACT

Background: The possibility of an association between the use of protease inhibitors (PI) by HIV/AIDS patients and the occurrence of T2DM mellitus (T2DM) is largely debated. Medicare recipients are disproportionately affected by T2DM.

Unfortunately, evidence is unavailable from that particular segment of the population.

Clinical management of HIV/AIDS is progressively expanding to include chronic/metabolic complications, which may pose a significant economic burden to both the patients and the Medicare system, which are disproportionately impacted.

Objectives: The aims of this project were to (1) examine the association between the use of PIs and the odds of developing T2DM among Medicare beneficiaries with HIV/AIDS, (2) assess any racial/ethnic disparity in odds of developing T2DM among Medicare beneficiaries with HIV/AIDS and (3) to determine the economic burden of comorbid T2DM among Medicare beneficiaries with HIV/AIDS.

Methods: This study used a nationwide Medicare claims data from 2013 to 2017 to analyze a sample of Medicare beneficiaries diagnosed with HIV/AIDS based on the International Classification of Diseases, Ninth & Tenth Revision, Clinical Modification (ICD-9/10-CM) codes. In study aim 1 and 2, a nested case-control study design was used to analyze the odds of developing T2DM among beneficiaries with HIV/AIDS.

HIV/AIDS positive beneficiaries enrolled continuously in Medicare Part A and Part B were included as well as those who never enrolled in a Health Maintenance Organization

(HMO) and those without a previous history of T2DM. A T2DM diagnosis was determined using T2DM specific ICD-9/10-CM codes. Two matched therapy group pairs – (PI versus non-PIs, PI versus no-ART) were generated using a 1:1 greedy Propensity Score (PS) matching procedure. Multivariate logistic regressions were performed to assess the odds of developing T2DM in both groups and for each race sub-group.

In study aim 3, a pooled cross-sectional study design was used to determine the economic burden of comorbidity T2DM in beneficiaries with HIV/AIDS. The analytical sample consists of HIV/AIDS positive beneficiaries enrolled continuously in Part A/B and never enrolled in an HMO. We assessed records of T2DM diagnosis using T2DM specific ICD-9/10-CM codes. Total medical costs, total prescription costs, total inpatient costs, total outpatient costs, total out of pocket (OOP) and total Medicare costs were assessed from Medicare claims and prescription drug files. Generalized linear models with a log-link and a gamma distribution were used to examine the impact of comorbid T2DM on different costs. All costs were adjusted to the 2017-dollar value using the medical component of a consumer price index based on Medical Expenditure Panel Survey (MEPS) guidelines.

Results: In study aims 1 and 2, the analytical sample consists of 2,353 beneficiaries with HIV/AIDS which includes 342 beneficiaries with T2DM, 2011 beneficiaries without T2DM, 1005 beneficiaries treated with PIs, 766 beneficiaries treated with non-PIs and 582 beneficiaries who had no-ART. Exactly 484 matched beneficiaries per therapy group was generated for PI versus non-PI pair and 490 beneficiaries per therapy group for the PI versus no-ART pair. Matched beneficiaries in the PI versus non-PI therapy group are mostly older 55 years and above per group, mostly male beneficiaries – 77.1% (n=373)

and consists mainly of Caucasians – 49% (n=237) and African Americans -45% (n=218) per group. Matched beneficiaries in the PI versus no-ART therapy group are mostly older than 55 years and above per group, mostly male beneficiaries – 75.9% (n=372) per group and consists mainly of Caucasians – 42.7 % (n=209) and African Americans -50% (n=245) per group. After adjusting for covariates: (1) in the PI versus non-PI pair: the odds of a T2DM diagnosis was higher among PI-users: AOR= AOR=1.76 [95% CI: 1.17-2.64], Caucasian PI-users: AOR=1.81 [95% CI: 1.02-3.22] and African-American PI-users: AOR= 1.86 [95% CI: 1.03-3.36] compared to non-PI users on average, and (2) in the PI versus no-ART pair: the odds of a T2DM diagnosis was higher among PI users AOR=1.87 [95% CI: 1.25-2.81], Caucasian PI-users: AOR=1.96 [95% CI: 1.14- 3.39] and African-American PI-users: AOR=2.05 [95% CI: 1.03-4.09] compared to ART naïve beneficiaries on average.

In study aim 3, a total of 2,509 eligible beneficiaries were identified of which 19.9 % (n=498) had T2DM and 80.2% (n=2,011) are non-T2DM beneficiaries. Beneficiaries with comorbid T2DM had a higher total prescription cost than non-T2DM beneficiaries across all costs: (mean total medical: T2DM beneficiaries (\$189,543) versus non-T2DM beneficiaries (\$124,052), $P < .0001$). After adjusting for covariates, compared to beneficiaries without comorbid T2DM, beneficiaries with comorbid T2DM had higher: **total hospitalization** cost: 63.34% (95% CI: 42.73% -86.94 %), **total outpatient** cost: 50.26% (95% CI: 30.70%-72.75%), **total OOP** cost: 59.15% (95% CI: 40.02%-80.92%), total **Medicare** cost: 27.95% (95% CI: 13.81%-43.84%) and total **medical** cost: 27.83% (95% CI: 14.27%-43.00%), compare to non-T2DM beneficiaries, on average.

Conclusion: Use of PIs is associated with a higher odd of T2DM diagnosis. Results are consistent within African Americans and Caucasian race-sub-groups; however, odds were higher among African Americans beneficiaries than Caucasians. Comorbid T2DM may impose a significant economic burden on Medicare beneficiaries with HIV/AIDS. The findings of this study suggest evidence-based risk management approach in the clinical use of PIs to avoid HIV treatment-related T2DM among Medicare population, who are already enormously predisposed as well as personalized risk management approach in the context of racial variation in treatment-related T2DM. The findings of this study could be helpful to the Medicare they seek to address concerns about its future financial solvency amidst a growing aging population and increasing per capita costs. Evidence of total OOP costs benefit the Medicare as they seek to reduce drug costs to benefit HIV positive beneficiaries who face high OOP cost.

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LIST OF ABBREVIATIONS

A1C	Glycated Hemoglobin
ACA	Affordable Care Act
ADA	American Diabetes Association
AIDS	Acquired Immunodeficiency Syndrome
ALS	Amyotrophic Lateral Sclerosis
ART	Antiretroviral Therapy
BEA	Bureau of Economic Analysis
CCI	Charlson Comorbidity Index
CCR5	Chemokine Receptor Antagonist
CD4	Cluster of Differentiation 4
CDC	Centers for Disease Control and Prevention
CGM	Continuous Glucose Monitoring
CMS	Centers for Medicare & Medicaid Services
CPI	Consumer Price Index
CRP	C-Reactive Protein

DAD..... Data Collection on Adverse Effects on Anti-HIV Drugs Cohort

DHHS..... Department of Health & Human Services

DME Durable Medical Equipment

DNA..... Deoxyribonucleic Acid

ESRD End Stage Renal Disease

FDA..... Food and Drug Administration

GLUT-4.....Glucose Transporter Type 4

HDL High-density lipoprotein

HIV Human Immunodeficiency Virus

INSTIs Integrase Strand-Transfer Inhibitors

IPTW..... Inverse Probability of Treatment Weighting

IRB..... Institutional Review Board

LIS..... Low Income Subsidy

MA-PDPMedicare Advantage Prescription Drug plan

MEPS.....Medical Expenditure Panel Survey

NCQANational Committee for Quality Assurance

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitors

NRTI.....Nucleoside Reverse Transcriptase Inhibitors

OOP..... Out of Pocket

PCEPersonal Consumption Expenditure Health Indexes

PDP	Prescription Drug Plan
PE	Pharmacokinetic Enhancers
PHC	Personal Health Care Index
PIs	Protease Inhibitors
PPAR	Peroxisome Proliferator-Activated Receptor
PSM	Propensity Score Matching
SAF	Standard Analytical Files
SNF	Skilled Nursing Facility
SSDI	Social Security Disability Insurance
T-CELL	Thymus lymphocytes
T2DM	Type 2 Diabetes Mellitus
TNF	Tumor Necrosis Factor
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

CHAPTER 1

INTRODUCTION

Anti-retroviral Therapies (ARTs) are very effective in viral suppression and immune system maintenance given that they act on different viral targets thereby ensuring a reduction in HIV-related mortality rates. However, the safety and tolerability of ARTs have been largely controversial. Butt and colleagues reported an increased risk of diabetes among veterans infected with HIV¹. A multicenter study shows that HIV-infected patients receiving Highly Active Anti-retroviral Therapy (HAART) are more than 4 times as likely to have an increased rate of diabetes than HIV-negative participants². Contrary to these studies, Dimala *et al.* recently conducted a study to compare the diabetes risk score in HIV/AIDS patients on HAART and HAART-naïve patients. Their findings showed no statistically significant association between HAART and diabetes³.

In addition to the on-going debate, evidence on the Medicare population is unavailable because the focus of previous studies has been on other population rather than the Medicare population, in whom the risk of diabetes is most prominent. Contrary to the public perception that HIV is an infection that mainly affects young adults, recent studies have revealed that the HIV epidemiology in individuals aged 65 and older has been changing and worsening dramatically in the past decades and this population constitutes over 85 percent of Medicare population.⁴

Racial disparities in access to HIV medications are an important determinant of racial variations in treatment outcomes and adverse medication related events. Racial disparities in receipt of HAART have been reported in previous studies ⁵. This was found to be true among Medicaid beneficiaries, which are expected to have equitable access to care given that Medicaid is structured to provide equal access to healthcare for all eligible enrollees. Racial disparity in access to care among patients enrolled in Medicaid may suggest a potential disparity in treatment related adverse events not only among the Medicaid population, but also among the Medicare population.

HIV infection, ART use, and age are important predisposing factors to metabolic syndromes such as diabetic comorbidity in HIV/AIDS. Comorbid diabetes in HIV patients is most likely to occur as treated patients grow older.⁶ These comorbidities may pose significant clinical challenges as well as an economic burden for the US Medicare system given the increasing number of surviving younger patients who will become eligible for Medicare in the nearest decade.⁷

1.1 Human Immunodeficiency Virus (HIV)

HIV is the virus that attacks the human T-cells, specifically the CD4 cells ,which protect the body from infection and other related foreign bodies.⁸ The HIV infection destroys the CD4 cells of the human hosts, thereby making the host's immune system weak or unable to fight against infections.⁸ Thus, the human host ultimately becomes more vulnerable to opportunistic infections.⁸ This can cause symptoms that signal Acquired Immune Deficiency Syndrome (AIDS) which is the last stage of HIV infection.⁸

HIV is classified into HIV-1 and HIV-2, which are different and can both result in AIDS.⁹ HIV-1 is the most common and most prevalent type of HIV globally. HIV-2 is less common and occurs in a much smaller number of people mostly from the West African regions.⁹ In the US, patients infected with HIV-2 constitute only about 0.01% of all HIV cases.⁹ It is harder to transmit HIV-2 between humans and it also takes a longer time for AIDS symptoms to manifest. HIV is spread through contact and exchange of certain bodily fluids with an infected person. Fluid contact or exchange mainly occurs during unprotected sexual contact or sharing of injection needles during medical treatment, blood transfusions, or drug abuse. It can also be transferred from an infected mother to her child through the placenta and breast milk.⁸

HIV infected person may experience any type of symptoms possible since the infection targets and impairs the immune system. Common symptoms that have been reported include fever and fatigue, sore mouth and throat, muscular aching, candida infection of the mouth, constant diarrhea, swollen lymph glands, seborrheic dermatitis and vaginal yeast infection.⁸ To detect the HIV infection, two major laboratory tests which involve a series of blood screenings may be conducted.⁹ Typically, the first test to be ordered by healthcare providers is the Enzyme Immunoassay (EIA), also referred to as the Enzyme-Linked Immunosorbent Assay (ELISA). ELISA detects HIV antibodies and antigens in the blood. It is recommended for individuals who have been exposed to HIV or those at high risk of contracting HIV.⁹ Following a positive ELISA test is the confirmation of HIV infection which is performed using the HIV differentiation assay.⁹ Two main laboratory indices may be used to monitor treatment progress in an HIV infection, namely: the CD4 count and the level of HIV RNA viral loads. A CD4 count

less than 500 count/ml indicates immune suppression while a high-level of HIV RNA viral loads indicates severe infection.⁹

1.2 Acquired Immunodeficiency Syndrome (AIDS)

AIDS represents the terminal stage of the HIV infection during which patients experience severe damage to the immune system and a resultant presence of numerous opportunistic infections in the host's system.¹⁰ According to the Centers for Disease Control (CDC), AIDS begins when HIV infected patients present with a CD4 cell count less than 200 count/ml.¹⁰ At this point the HIV/AIDS patients could experience illnesses such as pneumocystis carinii pneumonia, candida esophagitis, cryptococcal meningitis, AIDS dementia, toxoplasmosis encephalitis, progressive multifocal leukoencephalopathy, wasting syndrome, mycobacterium avium and cytomegalovirus infection.¹⁰ Currently, HIV/AIDS has no cure. However, available treatments do delay the progression of the disease, improves quality of life¹⁰, and increases life expectancy of HIV/AIDS patients to 70 years.¹¹

1.3 HIV/AIDS in The United States

In the United States (US), approximately 1.1 million people are living with HIV/AIDS, with approximately 37,600 new infections reported annually.¹² Although the importance of prevention and treatment has been met with huge government efforts, 1 in 7 of those infected are not aware that they have HIV virus.¹³ Over 700,000 people have died of HIV/AIDS related illnesses since the HIV epidemic began in the US in 1980s.¹² Although the size of the epidemic is small, relative to the entire US population,¹² it has continued to disproportionately impact certain population subgroups and regions. The

Southern region, in particular, is home to over 45% of US citizens currently living with HIV/AIDS, and accounts for about 50% of all new infections.^{12,14}

The HIV epidemic disproportionately impacts racial minorities, compared to the Caucasian majority.¹² The majority of new HIV/AIDS infections occur among African Americans and Hispanics.^{12,15} Out of 1.1 million people living with HIV in the US, 468,800 are African American; accounting for more people living with HIV than other ethnic groups.¹³ Furthermore, survival after an HIV diagnosis is lower in African Americans than among other racial groups. African Americans accounted for more than 50 % of HIV/AIDS related deaths in 2016.¹²

1.4 HIV/AIDS Treatment and Medications

Antiretroviral therapy (ART) represents different classes of medicines used in the treatment of HIV/AIDS. Eight classes of ARTs have been approved by the Food and Drug Administration (FDA) and most of the member classes are currently in use.^{16,17} The primary therapeutic goal of ART use is to achieve maximum and stable viral load suppression, restore and sustain the immune system and its functions, improve quality of life, and reduce HIV-related morbidity and deaths.¹⁷ As shown in table 1.1, FDA approved classes of ARTs include: Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), integrase strand-transfer inhibitors, fusion inhibitors, post attachment inhibitors, chemokine receptor antagonists and Pharmacokinetic Enhancers (PE).^{16,17}

1.4.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are effective against HIV-1 and HIV-2¹⁸ and act by interrupting HIV replication through competitive inhibition of the HIV reverse transcriptase enzyme disrupting the HIV DNA chain.¹⁹ The reverse transcriptase enzyme is a specific DNA polymerase that enables transcription of the HIV RNA into a double-strand pro-viral DNA. This DNA, upon elongation, is incorporated into the host-cell genome through the addition of purine and pyrimidine nucleosides.¹⁹ The NRTIs are structurally identical to the purine and pyrimidine nucleosides and are therefore incorporated into the pro-viral DNA chain, resulting in disruption of pro-viral DNA formation.¹⁹ NRTI was among the first of the ARTs to be approved for treatment of HIV/AIDS and they remain an integral component of the current standard treatment guidelines. The FDA approved seven classes of NRTIs which are currently in use including: abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine.²⁰ Several adverse effects reported with the use of NRTIs include: lactic acidosis, pancreatitis, hepatic steatosis, lipoatrophy and hepatic neuropathy.²⁰

Table 1.1 List of FDA approved single ART class

Brand Name	Generic Name (Other names)	Acronyms (other names)	FDA approval date
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)			
Ziagen	Abacavir sulfate	ABC	December 17, 1998
Emtriva	Emtricitabine	FTC	July 2, 2003
Epivir	Lamivudine	3TC	November 17, 1995
Viread	Tenofovir disoproxil fumarate	TDF (Tenofovir DF)	October 26, 2001
Retrovir	zidovudine	AZT, ZDV (Azidothymidine)	March 19, 1987
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Pifeltro	Doravirine	DOR	August 30, 2018
Sustiva	Efavirenz	EFV	September 17, 1998
Intelence	Etravirine	ETR	January 18, 2008
Viramune	Nevirapine	NVP	June 21, 1996
Viramune XR	Extended release Nevirapine		March 25, 2011
Edurant	Rilpivirine	RPV (rilpivirine hydrochloride)	May 20, 2011
Protease Inhibitors (PIs)			
Reyataz	Atazanavir	ATV (atazanavir sulfate,)	June 20, 2003
Prezista	Darunavir	DRV (darunavir ethanolate)	June 23, 2006
Lexiva	Fosamprenavir	FOS-APV, FPV (fosamprenavir calcium)	October 20, 2003
Norvir	Ritonavir	RTV	March 1, 1996
Invirase	Saquinavir	SQV (Saquinavir mesylate)	December 6, 1995
Aptivus	Tipranavir	TPV	June 22, 2005
Fusion Inhibitors			
Fuzeon	Enfuvirtide	T-20	March 13, 2003
CCR5 Antagonists			
Selzentry	Maraviroc	MVC	August 6, 2007
Integrase Inhibitors			
Tivicay	Dolutegravir	DTG, (Dolutegravir sodium)	August 13, 2013

Isentress	Raltegravir	RAL (Raltegravir potassium)	October 12, 200
Isentress HD			May 26, 2017
Post-Attachment Inhibitors			
Trogarzo	ibalizumab-uiyk	Hu5A8, IBA, Ibalizumab, TMB-355, TNX-355	March 6, 2018
Pharmacokinetic Enhancers			
Tybost	cobicistat	COBI, C	September 24, 2014

1.4.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are a class of ART that act by non-competitively binding on the p66 subunit at a hydrophobic pocket distant of HIV reverse transcriptase enzyme, thereby altering the active site and limiting viral activities.²¹ All NNRTI classes of ART exhibit similar mechanisms of action. Members of the NNRTI class include nevirapine, delavirdine, etravirine, rilpivirine, and efavirenz.²⁰ All member classes are effective against HIV-1 with etravirine having an additional activity against HIV-2.²² One commonly reported adverse event of NNRTIs is a rash, which manifests within the first few weeks of therapy and resolves as therapy continues.²⁰ Other adverse events include hepatotoxicity, insomnia, vivid dreaming, dizziness, hallucinations, and confusion.²⁰

1.4.3 Protease Inhibitors (PIs)

Protease Inhibitors (PIs) are a class of ARTs which act by competitively inhibiting the HIV protease enzyme responsible for the maturation of viral cells late in the viral cycle. The HIV protease enzyme facilitates the maturation of viral cells and peptide cleavage by directly binding onto the HIV protease enzyme. PIs prevent

subsequent cleavage of polypeptides and viral cell maturation.²³ They are effective against HIV-1 and HIV-2 clinical isolates.²³ Members of the PI class include ritonavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, amprenavir, lopinavir/ritonavir, and tipranavir.

1.4.4 Integrase Strand-Transfer Inhibitors (INSTIs)

Integrase Strand-Transfer Inhibitors (INSTIs) are known for their ability to competitively bind metallic ions in viral active sites to prevent the covalent linkage of pro-viral DNA to the cellular DNA.^{24,25} Members of the INSTI class include raltegravir, elvitegravir, and dolutegravir. Given that HIV integrase do not have human homolog, selective inhibition of target enzymes will result in a minimal number of adverse events.^{26,27} Commonly reported side effects include mild to moderate gastrointestinal effects and headaches.²⁰

1.4.5 Fusion Inhibitors

Fusion inhibitors extracellularly inhibit the fusion of HIV cells onto CD4 cells or other host targets, thereby preventing viral activities on the host.^{28,29} Due to the unique mechanism of action, fusion inhibitors are suitable in patients with high treatment resistance as its action provides an extra site for targeting viral cells.^{28,29} The most frequently used fusion inhibitor is enfuvirtide. Injection site reactions, subcutaneous nodules, erythema, pruritis, pains and ecchymoses are commonly reported adverse events.^{30,31}

1.4.6 Chemokine Receptor Antagonist (CCR5)

The only approved member class of Chemokine Receptor Antagonist (CCR5) is maraviroc, which is a prototype of CCR5.²⁰ Maraviroc selectively and reversibly binds the CCR5 co-receptor, thereby preventing the binding of the V3 loop and fusion of the HIV cellular membrane.³² It is active against tropical HIV-1 CCR5 and is associated with several commonly reported adverse events such as cough, pyrexia, dizziness, rash, musculoskeletal symptoms, abdominal pains, and upper respiratory tract infections.³³

1.4.7 Post-Attachment Inhibitors

Post-attachment inhibitors are indicated in HIV-1 multidrug resistance cases in which HIV is irresponsive to other ART regimens. Ibalizumab is the first class of post-attachment inhibitors approved by the FDA and is also the most recently approve ART.^{20,33} Ibalizumab is a monoclonal antibody which binds onto the extracellular domain 2 of viral cell receptors.²⁹ Conformational disruption associated with the binding of ibalizumab results in the prevention of coupling between gp120-CD4 complexes and CCR5 or CXCR4, which ultimately disallows viral entry and fusion.^{20,32} The most common side effects include diarrhea, dizziness, nausea, and immune reconstitution syndrome.³⁴

1.4.8 Pharmacokinetic Enhancers (PE)

The Pharmacokinetic Enhancers (PE) class of ARTs is often referred to as boosting agents and constitute only a single member class called cobicistat, which acts by inhibiting CYPE3A.²⁰ It is often used as a combination component with protease inhibitors in both treatment-naïve and treatment-experienced patients.²⁰

1.4.9 Combination Anti-Retroviral Therapy (cART)

Combination anti-retroviral therapy (cART) refers to the use of two or more antiretroviral drugs combined based on clinical recommendations for effective treatment of HIV/AIDS. Table 1.2 shows a list of FDA approved cART.^{16,17}

Table 1.2 List of FDA approved Combination Anti-Retroviral Therapy (cART)

Brand Name	Generic Name (Other names)	Acronyms (Other names)	FDA approval date
NRTIs Based cARTs			
Combivir	lamivudine and zidovudine	3TC / ZDV	September 27, 1997
Epzicom	abacavir and lamivudine	ABC / 3TC	August 02, 2004
Truvada	Tenofovir disoproxil fumarate and emtricitabine	FTC / TDF	November 17, 1995
Cimduo	Lamivudine and tenofovir disoproxil fumarate	3TC / TDF	February 28, 2018
Descovy	Emtricitabine and tenofovir alafenamide	FTC / TAF	April 04, 2016
Trizivir	Abacavir, lamivudine, and zidovudine	ABC / 3TC / ZDV	November 14, 2000
PI Based cARTs			
Kaletra	lopinavir and ritonavir	LPV/r, LPV / RTV	September 15, 2000
Multi-Class Combinations			
Atripla	Efavirenz, emtricitabine and tenofovir disoproxil fumarate	EFV / FTC / TDF	July 12, 2006
Complera	Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate	FTC / RPV / TDF	August 10, 2011
Evotaz	Atazanavir sulfate, cobicistat	ATV / COBI	January 29, 2015
Prezcobix	cobicistat, darunavir ethanolate	DRV / COBI	January 29, 2015
Stribild	elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate	QUAD, EVG / COBI / FTC / TDF	August 27, 2012
Genvoya	Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	EVG / COBI / FTC / TAF	November 05, 2015
Symfi Lo	Efavirenz, lamivudine, and tenofovir disoproxil fumarate	EFV / 3TC / TDF	February 05, 2018
Symfi	Efavirenz, lamivudine, and tenofovir disoproxil fumarate	EFV / 3TC / TDF	March 22, 2018

Delstrigo	Doravirine, lamivudine, and tenofovir disoproxil fumarate	DOR / 3TC / TDF	30-August-18, 2018
Julica	Dolutegravir and rilpivirine	DTG / RPV	November 21, 2017
Dovato	Dolutegravir and lamivudine	DTG / 3TC	April 9, 2019
Symtuza	Darunavir, cobicistat, emtricitabine, and tenofovir alafenamide	DRV / COBI / FTC / TAF	July 17, 2018
Biktarvy	Bictegravir, emtricitabine, and tenofovir alafenamide	BIC / FTC / TAF	February 17, 2018
Triumeq	Abacavir, dolutegravir, and lamivudine	ABC / DTG / 3TC	August 22, 2014

Since the introduction of cART in 1996, HIV management has improved significantly, resulting in improved mortality and morbidity. Evidence from clinical trials and observational studies has shown a significant reduction in morbidity and mortality among people with HIV/AIDs since the advent of cART.³⁵⁻⁴⁰ Over the last few decades, combination therapy has become better tolerated with simplified dosing (once daily fixed dose combinations) that improves compliance.^{35,41,42} cART fundamentally changed the epidemiology of HIV with the ability to confer stable suppression of HIV viral loads and boosting of the CD-4 cell counts.³⁷

According to the 2019 Department Of Health & Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (The Panel), effectiveness and preservation of future treatment options are key considerations in determining which classes of ARTs are combined as cARTs, as well as when a combination is used as a ‘preferred’ regimen or an ‘alternative’ regimen.⁴³ The choice of a cART regimen depends on the patients’ specific clinical conditions such as: the presence of transmitted HIV drug resistance, potential drug to drug interactions, expected adverse events, comorbidities,

socio-economic factors, and whether it is to be used for initial therapy or for ART-naïve patients.⁴³ A cART regimen is designated as a ‘preferred’ or ‘alternative’ regimen based on clinical trial evidence on efficacy in virologic suppression, tolerability, and toxicity profiles.⁴³ The ‘preferred’ cART regimen is designated for use in ART-naïve patients as well as ART-experienced patients who are initiating cART therapy. Conversely, a regimen designated as ‘alternative’ cART is used when there are comparative advantages in terms of either efficacy, resistance, tolerability, or potential for compliance, when compared to the preferred regimen.⁴³

Three main ART combination constituents were identified by the panel for initial therapy in ART-naïve patients. They include (1) NNRTI-based regimens, (2) Protease inhibitor-based regimens, and (3) Triple Nucleoside Transcriptase based-regimens.⁴³

The panel recommends the following NNRTI-based combinations:

- i) Efavirenz + (zidovudine or tenofovir or stavudine) + lamivudine as ‘preferred’ initial NNRTI-based regimens.
- ii) Efavirenz + (didanosine or abacavir) + lamivudine can be used as alternatives.
- iii) Nevirapine-based regimens can be used as alternatives.⁴³

Efavirenz containing cARTs are not to be used by pregnant women or women at reproductive age due to its teratogenicity properties.⁴³ NNRTI based combinations have a well-documented high anti-virologic, high immunologic efficacy and high potential for compliance and adherence due to their ease of use compared to the PIs.⁴³ They have fewer negative drug interactions compared to the PIs.⁴³ NNRTI based combinations are PIs sparing (i.e. preserve PIs use in case of resistance for NNRTI cARTs). One of the key

disadvantages is that resistance due to NNRTIs usually cut across the entire NNRTI member class.⁴³ The panel recommends lopinavir/ritonavir + (zidovudine or stavudine) + lamivudine as ‘preferred’ protease inhibitor-based regimens for use in PI-based combination regimens.⁴³ The panel recommends a 3-NRTI regimen which consists of the combination of abacavir, zidovudine (or alternately, stavudine), and lamivudine to be used only when other combinations such as a NNRTI-based, or a PI-based regimen cannot or should not be used as initial therapy for reasons such as important drug to drug interactions.⁴³

1.5 Type 2 Diabetes Mellitus (T2DM) in The Unites States

Diabetes is a chronic metabolic disorder characterized by insufficient insulin, a lack of insulin production, or muscular insensitivity to insulin, which is a naturally occurring hormone that helps in glucose utilization and metabolism.⁴⁴ Diabetes consists of three types: type 1 diabetes mellitus, type 2 diabetes mellitus (T2DM), and gestational diabetes. Type 1 diabetes is characterized by autoimmune destruction of the beta cell of the pancreas that produces insulin, thereby resulting in an insufficient amount of insulin or total lack of insulin in the body.⁴⁵ This condition is often hereditary, and patients require exogenous insulin intake to survive. T2DM is characterized by a combination of insulin deficiency and muscular insensitivity to insulin, resulting in the inability to stabilize and maintain normal blood glucose levels.⁴⁴ T2DM is the most common type of diabetes and occurs in about 90% of people with diabetes.⁴⁴

1.5.1 Epidemiology of T2DM in the United States

T2DM is one of the most prevalent chronic conditions and the seventh leading cause of deaths in the United States.⁴⁶ T2DM is a major risk factor for cardiovascular

disease and a leading cause of kidney failure, nontraumatic lower extremity amputations, and blindness among adults in the U.S.⁴⁶ In 2020, the National Diabetes Statistics Report noted that an estimated 34.2 million people in the U.S. are diagnosed with T2DM which represents about 10.5 % of the total population (all ages) and 2.8 % of the adult U.S. population. Over 1.5 million new cases of T2DM (7 in 1000 persons) were reported in 2015, of which 50 % were 45 to 65 years of age.⁴⁷ The economic burden of T2DM is high, with an estimated national cost of \$327 billion in 2017.⁴⁷ Approximately 73 % (\$237 billion) represents direct health care expenditures for T2DM, while 27 % (\$90 billion) were costs incurred due to overall lost productivity and diabetes related deaths.⁴⁷

1.5.2 T2DM management

The major goal in the treatment of T2DM is to control and maintain patients' blood glucose levels to a normal range using medications, good lifestyle habits, and diet. The first treatment approach for T2DM is weight reduction through T2DM diets and exercise. If symptoms and elevated blood glucose levels persist, diabetes medications including oral or injected dosage forms, are prescribed. Insulin is prescribed if elevated blood glucose levels persist after oral or injected anti-diabetes medication. Various classes of diabetes medications have been approved by the FDA: alpha-glucosidase inhibitors, amylin analogs, antidiabetic combinations dipeptidyl peptidase 4 inhibitors, incretin mimetics, insulin, meglitinides, non-sulfonylureas, SGLT-2 inhibitors, sulfonylureas, and thiazolidinediones.

In 2013, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) jointly recommended twelve management algorithms with the purpose of driving comprehensive management approaches for

T2DM.⁴⁸ This algorithm represents practice guides to clinicians with emphasis on the whole patient, his or her spectrum of risks and complications, and evidence-based treatment approaches.⁴⁸

The twelve recommended management algorithms include: (1) Continuous and effective lifestyle management with concurrent medical therapy, (2) Frequent blood glucose level monitoring to prevent therapy driven hypoglycemia and other risks that could lead to severe or non-severe hypoglycemia, (3) Both diet and weight-loss medication should be used to minimize the risk of obesity in order to prevent the progression of obesity-driven diabetes, (4) T2DM treatments and the hemoglobin A1C targeting should be individualized with a focus on the specific risk factors of the patient such as age, presence of other disease conditions, adherence to treatment and motivation level, time since first diabetes diagnosis, life expectancy, and risk of hypoglycemia. This is important because clinicians depend on patients for fasting and postprandial glucose monitoring and reporting, (5) An A1C level of $\leq 6.5\%$ is considered optimal in the management of diabetes, (6) Treatment with and choice of antidiabetic medication should be individualized based on the patient's specific risk factors and other attributes, (7) Other comorbidities such as cardiac and cerebrovascular conditions as well as kidney disease should be considered while choosing antidiabetic medication, (8) In the presence of these comorbidities, T2DM management should be comprehensive, (9) Speedy normalization of blood glucose levels and management of associated comorbidities and risk factors should be as fast as possible to slow and avoid further complications, (10) Costs of medication, management and potential for adherence in terms of types of dosage and form should determine choice of medication, (11) To individualize treatment and

achieve effective glycemic control, clinicians should utilize professional continuous glucose monitoring (CGM), and finally (12) In complying with these algorithms, all medication to be used should be FDA approved.⁴⁸

1.6 The Overview of Medicare and Healthcare Coverage

Medicare is the US national health insurance program established in 1965 to provide health care coverage primarily to elderly people 65 years old or older who have over 4 quarters of work credit. It was expanded in 1972 to additionally provide coverage for younger adults with disabilities who qualify for Social Security Disability Insurance (SSDI) and have received SSDI payments for at least 24 months. It also includes coverage for younger adults with End-Stage Renal Disease (ESRD) or Amyotrophic Lateral Sclerosis (ALS) (Lou Gehrig's disease).⁴⁹ Since expansion, Medicare has provided health and financial coverage for over 60 million beneficiaries including the elderly and those under 65 with long-term disabilities.⁴⁹

Most Medicare beneficiaries live with multiple chronic conditions and/or disabilities and survive on limited income. In 2016, reports on the financial and clinical characteristics of Medicare beneficiaries showed that over 50 % of Medicare patients had savings below \$74,450 and were living on incomes below \$26,200. The report also showed that about 32% of Medicare beneficiaries had a functional impairment, 25% were in poor health, 22% had multiple chronic conditions (often 5 or more), 15% were younger than 65 and had long term disabilities, over 12% were 85 years old and above, and 3% (about 3 million Medicare beneficiaries) live in long-term care facilities.⁵⁰

Medicare insurance provides coverage to beneficiaries through Part A, Part B, Part C and Part D insurance plans. Medicare Part A covers in-patient care services, Skilled Nursing Facilities (SNF), some home health services, and hospice care. Medicare Part B covers services such as physician visits, outpatient services, and some home health and free preventive services such as prostate cancer screening and mammography.⁵⁰ Part C, also known as the Medicare Advantage program, constitutes enrollment in private insurance plans such as health maintenance organization (HMO) or preferred provider organization (PPO) while also enrolled in Part A and Part B. These beneficiaries obtain prescription drugs through Part D.⁵⁰ Part D was established in 2006 and provides coverage for outpatient prescription drugs through contracting with private insurance plans that offer retail prescription drug coverage to Medicare beneficiaries.⁵⁰ Contracting private insurance plans includes stand-alone prescription drug plans (PDPs) which work alongside the original Medicare plans and the Medicare Advantage Plans with Prescription Drug coverage (MA-PDs). These are built into the Medicare advantage plan.⁵⁰ A summary of current deductible amounts and coinsurance rates for Part A and Part B over different kinds of healthcare service provision is listed in Table 1.3.⁵¹

Table 1.3: Summary of current Medicare Part A and Part B coverage and copays, 2020

Coverage	Patients Co-pay	Medicare Co-pay
Medicare Part A		
Hospital Care (Inpatient) i. Day 1 to 60 ii. Day 60 to 90 iii. Day 90+ (Lifetime Reserve Days) iv. Days after lifetime reserve days	i. \$1,408 deductibles ii. \$352 coinsurance per day iii. \$704 coinsurance per day iv. All cost	i. Balance ii. Balance iii. Balance iv. No cost
Skilled Nursing Facility Care i. First 20 days ii. Days 21 to 100 iii. Days after 100 days	i. No cost ii. \$176 iii. All cost	i. All cost ii. Balance t iii. No cost
Home Health Services Part-time or intermittent skilled nursing care, and or physical therapy	No Cost	All Cost
Hospice Care i. Palliative care (comfort care) ii. Prescription drug from outpatient iii. Inpatient respite care	i. No cost ii. \$5 per prescription iii. 5 % of the Medicare approved amount	i. All cost ii. Balance iii. Balance
Medicare Part B		
Medical Services Physician's services, Outpatient care Home health services, Durable medical equipment (DME), Mental health services, Other medical services	\$198 deductible 20% co-insurance if the doctor or other health care provider accepts assignment	Balance after \$198 deductibles
Durable Medical Equipment and Supplies	20% coinsurance for Medicare-approved amount after \$ 198 deductible is met.	Balance after \$198 deductibles
Outpatient Hospital Services	20% coinsurance for Medicare-approved amount after \$ 198 deductible is met	Balance after \$198 deductibles
Outpatient Medical and Surgical Services and Supplies	20% coinsurance for Medicare-approved	Balance after \$198 deductibles

X-rays, casts, stitches, outpatient surgeries	amount after \$ 198 deductible is met	
Laboratory tests Blood test, urinalysis, Human Papillomavirus, Lab pap test, colorectal screening, hepatitis C, HIV test etc.	No cost	100 % of the cost of the approved
Breast Cancer Screening: Mammogram i. Once a year for women 35-39 years old ii. More than once a year	i. No cost ii. 20% coinsurance for Medicare-approved amount after \$ 198 deductible is met	i. 100 % cost ii. Balance after \$198 deductibles
Home Health Services Medical social services, part-time or intermittent home health aide services, DME and medical supplies for use at home	No cost	100 % of the cost of the approved care

1.6.1 Medicare Population and HIV/AIDS

Medicare is an important source of health coverage for people with HIV. It is currently the largest source of federal government healthcare spending on HIV, providing health coverage for one quarter of all HIV patients currently under care.⁴⁹

1.6.1.1 Epidemiology of HIV/AIDS among the Medicare population

In 2014, 0.4% of all Medicare beneficiaries with fee-for-service redeemed claims for HIV/AIDS treatment.⁵² The prevalence of HIV/AIDS in the US has increased over time owing to the availability of earlier diagnoses, improved therapy, and steady incidence rate.^{53,54} As the number of HIV/AIDS survivors increases following advancements in treatment, and a steady number of new infections grows, the number of Medicare beneficiaries living with HIV/AIDS also increases. The number of Medicare

beneficiaries with HIV rose from 42,500 in 1997 to 120,000 in 2014.⁴⁹ Consequently, the number of diagnosed and undiagnosed elderly Medicare beneficiaries has also increased because a large segment of the HIV population has grown older and now qualifies for Medicare.⁴⁹ Approximately 21% of Medicare beneficiaries with HIV are elderly (65 years and above) and qualify for Medicare based on age only. The remaining 79% includes younger, disabled individuals who qualify for Medicare based on disability and are receiving SSDI payments.⁴⁹ However, it has been estimated that over 50% of the individuals with HIV will be over 50 years of age in the near future⁵⁵, thus indicating an upward trajectory in the prevalence of HIV among the elderly population.

In addition, unprotected sexual behavior still plays a huge role in HIV infection among the elderly who are sexually active late into life.^{56,57} Elderly individuals are generally perceived as a low-risk population, and consequently, providers often do not routinely collect and record their sexual habits and activities. In the same vain, elderly people don't readily share their sexual habits with providers.^{55,58,59} Furthermore, the physiology of the older population changes in ways that increase susceptibility to HIV infection among those that remain sexually active. Post-menopausal women do not worry about becoming pregnant and are more likely to have unprotected intercourse.^{58,60} Age related thinning and dryness of the vaginal epithelium can expose vaginal epithelial tissues to abrasions, and consequently facilitate HIV infection.⁵⁸ It has been shown that the postmenopausal cervix may undergo immune changes, producing target cells such as CD4+ and CCR5+ T-cells with a greater number of inflammatory factors which facilitates HIV acquisition and replication.^{61,62}

Racial disparity in the prevalence of HIV/AIDS among Medicare beneficiaries has been reported. Medicare beneficiaries with HIV are disproportionately African American. They have the highest prevalence of infection (1.6%), followed by Hispanics (0.8%), and Indian/Alaska Native (0.4%). Caucasians and Asian/Pacific Islanders had the lowest prevalence of all races (0.2%).⁵² Other relevant demographic disparities have also been recognized. Medicare beneficiaries with HIV are disproportionately men (74%) and mostly dual eligible for both Medicaid and Medicare (69%).⁴⁹

1.6.1.2 Health care benefits for HIV-positive Medicare beneficiaries

Medicare provides a wide range of coverage for several healthcare services such as hospital care, medical care and physician visits, and prescription drugs. However, under the traditional Medicare Parts A and B, beneficiaries with HIV/AIDS are not covered for all the necessary health care services. Also, there is no OOP expenditure cap associated with Medicare parts A and B. As a result, the Medicare Part D plan provides much needed cost-sharing assistance specifically for Medicare beneficiaries with conditions that involved treatment with costly medications, including those with HIV. Part D subsidizes prescription drug costs for beneficiaries enrolled in private plans through low income subsidy (LIS) programs with catastrophic benefits. In 2014, approximately 77 % of Medicare beneficiaries with HIV qualified for the LIS program.

Consistent with the Center for Medicare and Medicaid (CMS) guidelines and the Affordable Care Act (ACA) codified law which designated Anti-retroviral therapy (ART) as one of the ‘six protected’ drug classes, Medicare Part D plans are required to cover all ARTs including those in the coverage gaps.⁴⁹ In addition to ARTs coverage, Medicare provides risk-based coverage for preventive measures such as HIV laboratory tests and

screening. Medicare provides coverage for once-a-year voluntary HIV tests for Medicare beneficiaries within the age range of 15 to 65 years old and pregnant beneficiaries, regardless of the risk of HIV infection. Beneficiaries younger than 15 and older than 65 are only covered if they are at increased risk of HIV infection.⁴⁹

In addition to Medicare benefits, HIV positive beneficiaries benefit from supplemental health coverage from Medicaid, the Ryan White HIV/AIDS Program,⁶³ and other payers. Low income dual eligible beneficiaries benefit from Medicaid supplemental coverage for premiums and cost sharing.⁴⁹ Eligible beneficiaries may receive payments of health coverage expenses from the Ryan White HIV/AIDS Program and additional services, such as case management and transportation assistance. Specifically, the Ryan White HIV/AIDS Program provides primary medical care, social support services, as well as funding of medications for low-income HIV patients who may be underinsured.⁶³ The program is committed to reducing HIV transmission among HIV positive patients living in hard-to-reach areas. This is accomplished through grant provisions for HIV care to relevant local communities and states, medication provision, and prevention education and aids to reduce transmission.⁶³ More than 50 % of people with HIV receive HIV treatment and care from the Ryan White HIV/AIDS Program, which means that over 500,000 patients receive HIV care and services through the program annually.⁶³

1.6.1.3 Medicare spending on HIV

Since the beginning of the HIV epidemic, the combined global and domestic federal expenditure for HIV has risen to \$34.8 billion in the 2019 fiscal year.⁶⁴ Growth in domestic expenditure has been largely driven by Medicaid and Medicare through

mandatory treatment policies.⁶⁴ Medicare has surpassed Medicaid in funding for HIV over the years due to the growing number of HIV patients who survive the infection reaching the age of eligibility for Medicare. Since the introduction of Medicare Part D which provides cost sharing assistance to Medicare beneficiaries and dual eligible with HIV, Medicare has become the agency of the federal government with the largest source of funding for HIV care.⁴⁹ In the 2016 fiscal year, 2% of Medicare expenditures were directed toward HIV care, which is a total of \$10 billion. This represents approximately 51% of all federal spending on HIV care. In 2014, the average Medicare per capita spending for Medicare beneficiaries was \$45,489 of which 59% (\$26,761) constituted prescription drug spending through Part D Medicare plans.⁴⁹ It is worthy of note that annual per capita Medicare spending in 2014 was significantly higher among Medicare beneficiaries who are recipients of Low Income Subsidy (LIS) compared to those who are not.⁴⁹

1.6.2 Medicare population and diabetes

In a study conducted by Andes *et al* which exclusively used Medicare data for 1999-2017 showed that the national prevalence of diabetes among Medicare fee-for-service beneficiaries rose from 23.3% in 2001 to 31.6% in 2015.⁶⁵ Prevalence varies among beneficiaries of different racial identification. African Americans, Hispanics and Asian/Pacific Islanders have prevalence rates that are significantly higher than the national prevalence rate, while the Caucasian Medicare beneficiaries have a prevalence below the national prevalence rate- 29.2%.⁶⁵ African-Americans have the highest prevalence (47.4), followed by Hispanics (46.3) and Asian/Pacific Islanders (43.5) compared to Caucasian Medicare beneficiaries. Cases of new diabetes diagnoses were

recorded at the rate of 3.0% in 2015 across all ethnicities.⁶⁵ Incidence rates vary across race according to Andes *et al*, with incident rates among Hispanics being (5.2%), African Americans (5.1 %) and Asian/Pacific Islanders (4.7 %). All of these were well above the national incidence rate of 3.0%, whereas the Caucasian Medicare beneficiaries incidence rate (2.8 %) was below the national rate.⁶⁵ Among beneficiaries aged 68 and above, the overall prevalence and incidence of diabetes were 31.6% and 3.0% respectively. ⁶⁵

Gender disparity in national prevalence and incidence rates were also reported. Men have a higher national prevalence rate (34.3) and incidence rate (3.5) than women. This variation was sustained from 2001 through 2015. ⁶⁵ When assessing the modifier effect of race on prevalence rates among men and women, results showed that the prevalence rate was higher in men among Caucasians and Asians/Pacific Islanders, and higher in women among African Americans and Hispanics. ⁶⁵

1.6.2.1 Medicare coverage and spending for T2DM

Generally, Medicare Part B and Part D provide coverage for medications and necessary supplies needed for diabetes management. Medicare Part B covers fasting blood glucose screening once a year and two times a year for high risk beneficiaries. High risk beneficiaries are those with a genetic family history of diabetes and those with other chronic conditions that are risk factors to diabetes – high blood pressure, obesity, history of pre-diabetes (abnormal tri-glyceride levels and history of high blood sugar levels), and abnormal cholesterol.

As described in Table 1.3, beneficiaries with diabetes are not charged for screening if their physicians accept Medicare approved amounts but may be charged a

20% copay for the doctor's visit. Medicare Part B also covers supplies such as sugar monitoring equipment, lancet devices and lancets, blood sugar test strips and solutions. Medicare may cover external insulin pumps and insulin DME, and medical nutritional therapy for diabetes, however, patients may pay 20% of the Medicare approved amount after the yearly deductible as shown in Table 1.3. For beneficiaries with high risk, Medicare Part B provides coverage for the initial 10-hour diabetes self-management education and training, as well as a two-hour post training follow up each year. During complications such as foot diseases, Medicare Part B provides coverage for professional foot care every six months (so long as the beneficiary did not visit a footcare professional for another reason) and special footwear.

Medicare Part D provides coverage for diabetes medications and supplies for enrolled beneficiaries with diabetes. Diabetes medications covered include various classes of antidiabetic medications such as sulfonylureas, biguanides, thiazolidinediones, alpha glucosidase inhibitors, and injectable insulin which are not associated with insulin infusion pumps (Medicare Part B covers insulin administered with insulin infusion pumps as DME). Medicare Part D may also cover insulin associated supplies such as syringes and needles, gauze and alcohol swabs. Medicare beneficiaries on Part D may pay certain coinsurance or Part D deductibles depending on which private plan they are enrolled in - PDP or MA-PDP.

Medicare beneficiaries with diabetes experience significant challenges and financial burdens regarding access to care and OOP expenses.⁶⁶ The increasing cost of prescription drugs for different disease conditions, including diabetes, has been a huge concern to policy makers. Specifically, the cost of insulin has been shown to drive up

patient and Medicare expenditure for diabetes. Between 2007 and 2017, expenditure on insulin alone by Medicare, private insurance plans, and patients has risen from \$1.4 billion to \$13.3 billion.⁶⁶ This translates to an increased cost from \$862 in 2007 to \$3,949 per insulin user which represents about a 358 % increase.⁶⁶ Considering the increased number of Medicare beneficiaries using insulin and the increased price of insulin, the aggregate total OOP expenditure increased from \$236 million to \$968 million between 2007 and 2016. This represents an 81% increase in OOP expenditure per beneficiary between 2007 and 2016 (\$324 to \$588).⁶⁶

1.7 HIV Infection, Treatment and Metabolic Syndrome.

Diabetes and complications of glucose metabolism are associated with HIV infection and treatment.⁶⁷ Three different kinds of patients exist based on when diabetes or HIV were diagnosed. Some patients were diagnosed with diabetes at the onset of HIV, some have pre-existing diabetes before HIV diagnosis, and some developed diabetes or have signs of diabetes after the initiation of ART.⁶⁸ The underlying pathogenesis of metabolic dysregulation is different among these groups of patients.⁶⁸

After HIV diagnosis, HIV patients commonly present with metabolic dysregulation such as dyslipidemia, lipodystrophy, metabolic syndromes and dysregulated glucose metabolism.⁶⁸ In addition to HIV infection, HIV patients are predisposed to the same risk factors for T2DM and metabolic syndrome. These risk factors include older age, duration of HIV infection, high viral load, low CD4 count, being a male, high waist/hip ratio, and ethnicity.^{69,70} Furthermore, impaired glucose tolerance and insulin resistance are key parts of diabetes pathogenesis in patients with HIV infection.⁶⁹⁻⁷³ The major contributors to metabolic syndrome in HIV/AIDS are

iatrogenic. Anti-retroviral-related T2DM, lipodystrophy, and metabolic dysfunction including insulin resistance have been reported to have increased among patients treated with ARTs.⁷⁴

HIV patients could have an effective viremic control but may be highly predisposed to metabolic syndrome. This is explained by the interaction between HIV infection, antiretroviral therapy (ART), and inflammation. Figure 1.1 shows the interaction between HIV infection, HIV treatment with ARTs and inflammation, which independently and collectively result in several chronic conditions such as cardiovascular disease, dyslipidemia, insulin resistance, and lipodystrophy.⁷⁵ There is existing evidence that shows that the activation of the immune system following either HIV infection or treatment with ART is associated with insulin resistance.⁷⁵

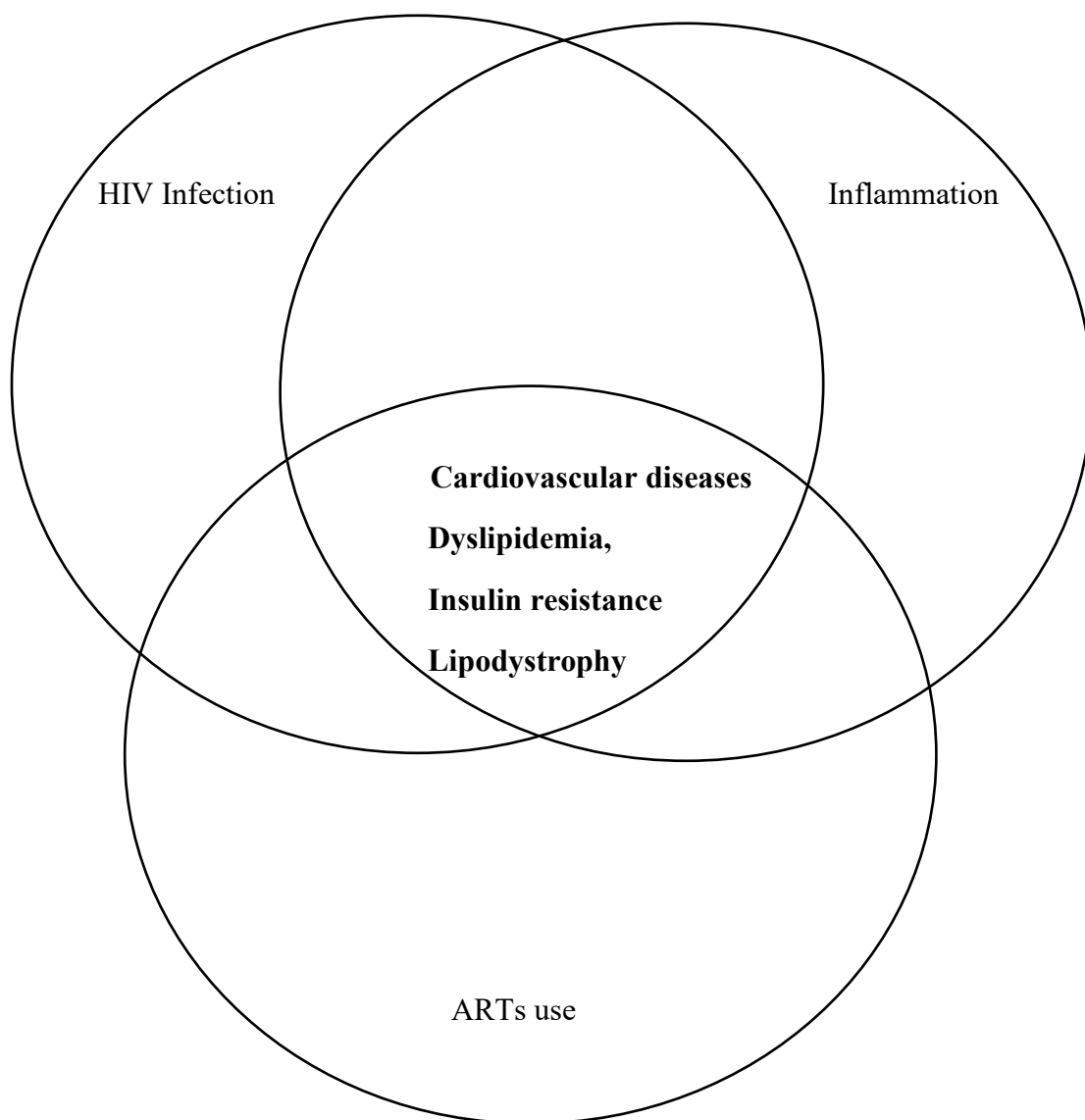


Figure 1.1: Interrelationship of HIV infection, ARTs, and inflammation with metabolic syndrome.

1.7.1 Biology of HIV infection, ARTs, and metabolic syndrome

According to the World Health Organization's (WHO) provisional report, metabolic syndrome consists of a combination of metabolic dysfunctions resulting from insulin resistance, obesity and impaired glucose regulation manifesting as impaired glucose tolerance.⁷⁶ Typically, the presence of at least five metabolic dysregulation components such as elevated triglyceride levels and blood glucose levels, central obesity, high blood pressure and decreased high density lipoprotein levels constitutes metabolic syndrome diagnosis.⁷⁷ The cascade of physiological processes that triggers metabolic syndrome involves factors such as peroxisome proliferator-activated receptor gamma (PPAR), tumor necrotic factor-alpha (TNF), adipose tissue, interleukins, fuel oxidation, and insulin secretion dysfunction.⁷⁸

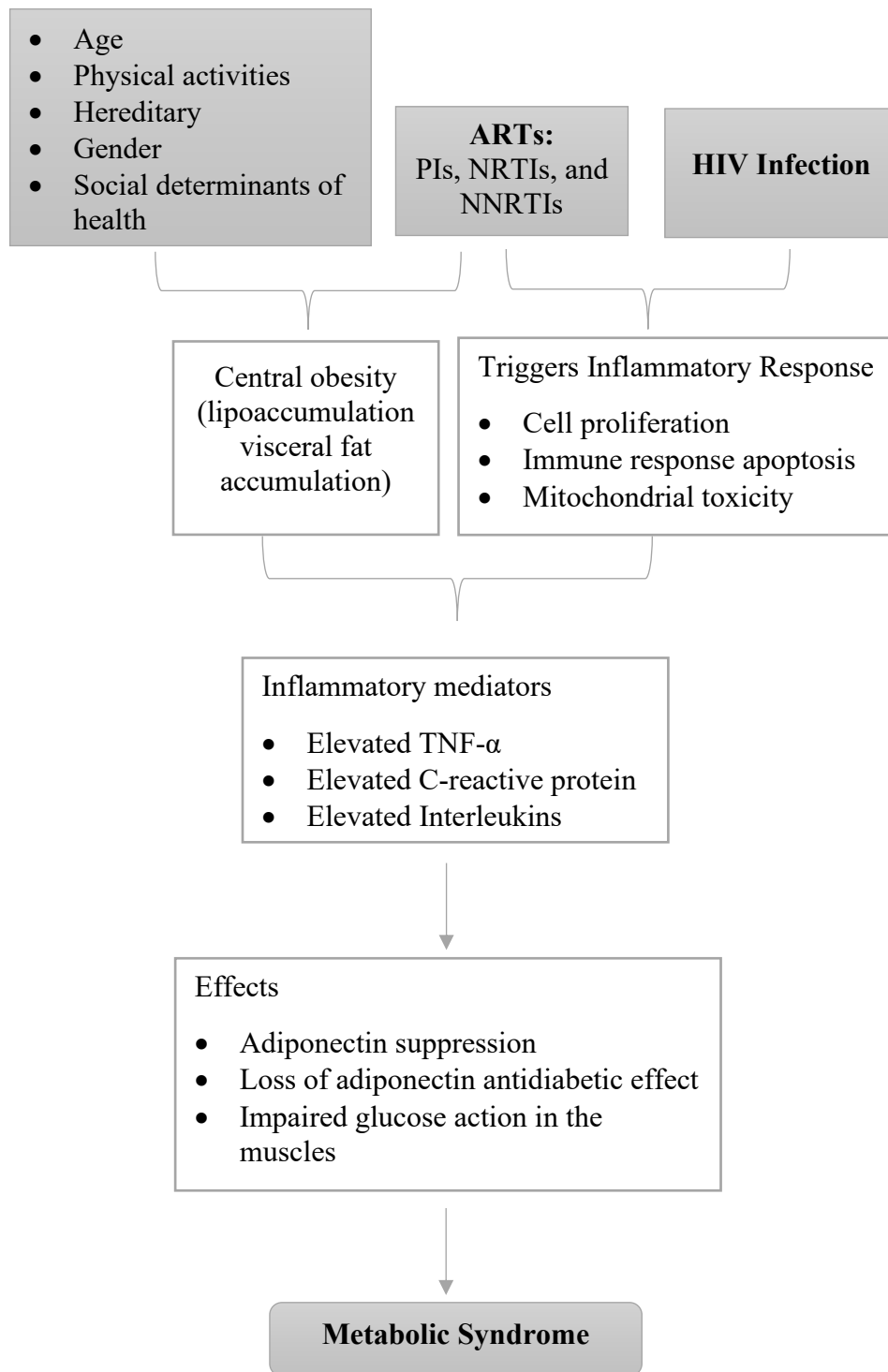


Figure 1.2: Pathophysiology of metabolic syndrome from HIV infection, ARTs and other factors

1.7.1.1 Metabolic syndrome and HIV infection

HIV infection is associated with metabolic syndrome through two major physiological pathways which include, (1) cellular apoptosis and the body's inflammatory response to the HIV infection which leads to insulin resistance and, (2) Mitochondria dysfunction induced by cell apoptosis.

HIV specific inflammatory markers have been implicated in several chronic disease conditions including T2DM.⁷⁹ In addition, the body's response to inflammation results in the suppression of anti-diabetic functions of adiponectin, thereby impairing tissue sensitivity to insulin leading to hyperglycemia and T2DM.⁸⁰ Cellular apoptosis involves the binding of the HIV proteins gp120 and gp41 to the CD4/CXC chemokine receptor 4, thereby mediating apoptosis through the fusion/hemifusion process referred to as gp4 induced hemifusion.⁸⁰ Studies have shown that gp41 induced hemifusion derives virion-induced apoptosis which triggers inflammatory mediators such as, TNF- α , interleukins and C-reactive protein (CRP) levels, which are associated with impaired muscle response to insulin and adiponectin suppression (an adipose-specific collagen-like molecule with anti-diabetic activity) thereby resulting in T2DM development.⁸¹

Cytotoxic protease secreted during HIV infection causes apoptosis through cellular proteins such as actin, Bcl2, and procaspase.⁸⁰ Activation of cytotoxic proteases depends on cytochrome c which is exclusively domicile in the mitochondria.⁸⁰ During activation following apoptotic signal, ions in the mitochondria are distributed asymmetrically on both sides of the internal sections of the mitochondria membrane.⁸⁰ The mitochondrial permeability transition pore complex (PTPC) opens, resulting in the loss of trans-mitochondrial potential and mitochondrial disruption.⁸⁰ This leads to the

release of apoptogenic factors which includes the cytochrome c and procaspase-9.^{82 83}

Mitochondrial disruption and subsequent host cell apoptosis which results from uncontrolled release of cytochrome c triggers host inflammatory response.⁸² The inflammatory response involves the release of inflammatory mediators, such as interleukins and C-reactive protein (CRP), at levels which suppress adiponectin⁸³ and induce muscular insulin resistance⁸² resulting in metabolic syndrome (Figure 1.2).

1.7.1.2 Metabolic syndrome and ARTs

The use of ART and its combination regimens has shown great clinical benefits in HIV treatment. However, long term use has been associated with metabolic syndrome as an adverse event. Furthermore, the use of these therapies can trigger a cascade of activities that results in the development of dyslipidemia, lipodystrophy and mitochondrial dysfunction. Specifically, ARTs stimulates an increased release of TNF- α which contributes to the impairment of fatty acid metabolism, lipid oxidation, and suppression of lipolysis.⁸⁴ This impact on lipid metabolism results in altered fat distribution and major alterations in the lipid profile, which is characterized by an increase in the levels of triglycerides (hypertriglyceridemia), a low-density lipoprotein cholesterol, and a decrease in HDL cholesterol.⁸⁵ Altered glucose homeostasis has also been reported during HIV treatment with ARTs. *In vitro* studies suggested a physiologic process that involves an insulin sensitive glucose transporter that is responsible for glucose uptake - GLUT-4. Indinavir inhibits GLUT-4, thereby preventing muscular and adipocyte's glucose uptake.^{86,87} Although all member classes of PIs inhibit GLUT-4, several studies have reported that atazanavir did not inhibit GLUT-4.^{87,88} Metabolic

syndrome develops in patients treated with ARTs through two major pathways which may include lipodystrophy, dyslipidemia, and mitochondria dysfunction.

Lipodystrophy and dyslipidemia are the two major clinical manifestations of metabolic syndrome. Lipodystrophy results from ART and HIV infection induced alterations in lipid metabolism⁸⁹ while dyslipidemia is characterized by hypertriglyceridemia, hypercholesterolemia, and low levels of HDLs⁹⁰, which results from impaired lipoprotein metabolism.⁹¹ PI related metabolic syndrome occurs due to PI-induced alteration in the expression of sterol regulatory element-binding protein-1 and PPAR- γ which are key elements required for cellular adipocytes differentiation.⁹² Thus, in the process, cellular adipocytes differentiation is inhibited which leads to impairment of lipid metabolism and consequently lipodystrophy and dyslipidemia.⁹² Along the line, dyslipidemia and hyperglycemia develop as well as hypertriglyceridemia.

Hypertriglyceridemia is known to be associated with acute pancreatitis which is characterized by beta cell function disruption and the subsequent development of T2DM.⁹³ Another pathway through which use of ARTs could be linked to metabolic syndrome is mitochondrial toxicity or mitochondrial disruption which involves polymerase- γ hindrance and draining of mitochondrial deoxynucleic acid (DNA).⁹⁴ Mitochondrial disruption results in insulin resistance which potentially leads to T2DM

CHAPTER 2

LITERATURE REVIEW

First, this chapter presents the literature review of relevant peer reviewed articles that evaluated HIV treatment with PIs and the risk of developing T2DM. Reviewed studies were cross-sectional studies, case-control studies, cohort studies, and randomized control trials. The characteristics of these studies are summarized in Table 2.1 and Table 2.2. Second, this chapter reviews literature regarding the disparity in race/ethnicity as applies to the risk of developing T2DM among HIV/AIDS positive patients treated with PIs. Third, this chapter details the review of literature regarding additional costs of T2DM comorbidities among patients with HIV/AIDS. Finally, the study objectives, specific aims, and hypothesis as well as significance and innovation are discussed in this chapter.

2.1 Protease Inhibitors and Development of T2DM

The safety and tolerability of protease inhibitors (PI) has been widely investigated and findings are largely controversial in terms of the risk of T2DM, insulin resistance and related metabolic syndromes. Table 2.1 summarizes some characteristics of studies that report that use of PIs is associated with the risk of T2DM. Among reviewed cross-sectional studies, Barry *et al* studied 164 HIV patients and compared patients on PI-based combination therapy with those on non-PI based combination therapy. They found that patients on PI-based combinations had greater triglyceride changes than non-PI based

combinations and their seronegative counterparts.⁹⁵ Furthermore, Behrens *et al* showed that PI-based ART combinations were significantly associated with impaired glucose tolerance. Non-combination PI-based ART and their associations with the risk of T2DM have also been widely explored.⁹⁶ Andrew Carr *et al* compared the occurrence of peripheral lipodystrophy, hyperlipidemia, and insulin resistance in 116 patients receiving protease inhibitors versus 32 HIV patients who are protease inhibitor naïve.⁹⁷ They found that protease inhibitor therapy was associated with significantly higher triglyceride levels.⁹⁷ Maganga *et al* compared the risk of glucose metabolism disorder among HIV positive ART-naïve patients and HIV positive patients on various ARTs, such as lopinavir and ritonavir, nevirapine, efavirenz, tenofovir, stavudine, zidovudine and seronegative patients. This finding indicates that patients on ARTs have 5-fold greater odds of having glucose metabolism disorder compared to ART-naïve groups and seronegative patients.⁹⁸ Samaras *et al* reported that HIV patients receiving protease inhibitors were more commonly presenting with metabolic syndrome, which is associated with a nine fold prevalence of T2DM.⁶

In a case-control study conducted in Taiwan, 1,534 HIV patients enrolled in a prospective cohort study and were followed for 14 years.⁹⁹ Out of the eligible 824 HIV positive patients, only 50 patients developed diabetes. Lo *et al* matched two controls per case and they found that exposure to protease inhibitors were significantly associated with diabetes.⁹⁹

Table 2.1: Characteristics of selected studies that reported significant association between use of PIs and T2DM

Author (Years)	Study title	Data source	Study design	Sample size	Treatment	Outcomes	Results
Barry (2014) ⁹⁵	HIV, Metabolic Syndrome X, Inflammation, Oxidative Stress, and Coronary Heart Disease Risk	Miami Veterans Administration Medical Center Health Records	Cross-sectional	164	HAART	Fasting blood glucose	Use of PI based HAART was associated with greater triglyceridemia, and lipidemia than it was for non-PI-exposed HIV+ subjects,
Behrens (1999) ⁹⁶	Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors	Laboratory results of participants	Cross-sectional	49	PI based ART combinations	Oral glucose tolerance test (OGTT)	PI are use is associated with impaired glucose tolerance and hyperproinsulinemia
Carr (1998) ⁹⁷	A syndrome of peripheral lipodystrophy, hyperlipidemia and insulin resistance in patients receiving HIV protease inhibitors	Laboratory results of participants	Cross-sectional	195	PIs	Fasting blood glucose	Use of PI was associated with hyperlipidemia and insulin resistance
Maganga (2015) ⁹⁸	Glucose Metabolism Disorders, HIV and Antiretroviral	Bugando Medical	Cross-sectional	454	ART	Oral glucose tolerance test (OGTT)	HIV-infected adults on ART had a higher risk of diabetes (OR

	Therapy among Tanzanian Adults	Centre HIV clinic					= 5.72 (2.78–11.77), $p < 0.001$) than HIV-negative adults.
Samaras (2007) ⁶	Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected]ccc hypoadiponectinemia	Cross-sectional lipodystrophy case definition cohort	Cross-sectional	788	HAART	International Diabetes Federation definition of metabolic syndrome	Metabolic syndrome was more common in those currently receiving protease inhibitors ($P = 0.04$)
Lo (2009) ⁹⁹	Risk factors for incident diabetes mellitus among HIV-infected patients receiving combination antiretroviral therapy in Taiwan: a case-control study	National Taiwan University Hospital	Case-control	824	PIs	Diagnosis diabetes	Current use of protease inhibitors is associated with Incident DM (OR 2.528; 95% CI 1.186-5.389)

Capeau (2012) ⁷⁴	Ten-year diabetes incidence in 1046 HIV-infected patients started on a combination antiretroviral treatment	47 French clinics	Cohort	1046 patients	PIs	Fasting blood glucose	The incidence of diabetes was associated with short-term exposure to indinavir (0–1 year: hazard ratio = 2.53)
Ledergerber (2007) ¹⁰⁰	Factors Associated with the Incidence of Type 2 Diabetes Mellitus in HIV-Infected Participants in the Swiss HIV Cohort Study	Swiss HIV Cohort Study	Cohort	8253	PIs and NRTIs	Type 2 diabetes	PIs and was associated with the risk of developing type 2 diabetes mellitus
Squillace (2016) ¹⁰¹	Triglyceride/HDL ratio and its impact on the risk of diabetes mellitus development during ART	Icona Foundation study	Cohort	3546	PIs and other ARTs	Type 2 diabetes	PI (atazanavir/ritonavir) is associated with DM (1.30; CI 95 % 7.98)
Tsiodras (2000) ¹⁰²	Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and	outpatient and inpatient medical records	Cohort	221	PI and NRTI	Type 2 diabetes	PIs were independently associated with hyperglycemia AIRR, 5.0; 95%

	lipodystrophy: a 5-year cohort study						[CI], 1.3-19.4), and hypertriglyceridemia AIRR, 6.1; 95% CI, 3.1-11.7)
Hughes (2005) ¹⁰³	Risk factors for new-onset diabetes mellitus in patients receiving protease inhibitor therapy	Northern Alberta HIV program	Cohort	496	PI	Type 2 diabetes	PI is significantly associated with developing DM (OR 1.52, 95% CI 1.07 to 2.17; P=0.02)
Justman (2003) ¹⁰⁴	Protease inhibitor use and the incidence of diabetes mellitus in a large cohort of HIV-infected women	Six inner-city clinical sites in the United States	Cohort	1785	PI and NRTI/NNRTI	Type 2 diabetes	Multivariate models identified PI use [HR] = 2.90 [95% CI: 1.50-5.60]
Carr (1999) ¹⁰⁵	Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidemia, and diabetes mellitus: a cohort study	St Vincent's Hospital	Cohort	113	PI	Type 2 diabetes	Impaired glucose tolerance occurred in 16% of protease-inhibitor recipients and diabetes mellitus in 7%
Calza (2003) ¹⁰⁶	Incidence of hyperlipidemia in a cohort of 212 HIV-infected patients receiving a protease	Tertiary hospital	Cohort	212	PI	Fasting blood glucose	PI use show statistically significant increase in serum triglyceride levels (P<0.005)

	inhibitor-based antiretroviral therapy						
Mulligan (2000) ¹⁰⁷	Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection	University of South California	Cohort	29	PI	fasting glucose; insulin; triglycerides	Changes in glucose and lipid metabolism are induced by PI therapy
Tripathi (2015) ¹⁰⁸	Incidence of diabetes mellitus in a population-based cohort of HIV-infected and non-HIV-infected persons: the impact of clinical and therapeutic factors over time	Medicaid	Cohort	6816	PI and other ARTs	Type 2 diabetes	A significantly higher risk of diabetes with cumulative exposure to PI (adjusted relative risk 1.35. 95% CI 1.03–1.78),
Salehian (2005) ¹⁰⁹	Prevalence and incidence of diabetes in HIV-infected minority patients on protease inhibitors	Inner-city HIV outpatient clinic	Cohort	101	PI	Type 2 diabetes	PIs increase the likelihood of diabetes developing
Woerle (2003) ¹¹⁰	Mechanisms for the deterioration in glucose tolerance associated with HIV	Infectious Disease Clinic	RCT	27	PI	Type 2 diabetes	PI regimens impair glucose tolerance in patients infected with HIV

	protease inhibitor regimens						
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Among reviewed cohort studies, Capeau *et al*, followed 1,046 patients in France and found that short-term exposure to indinavir is associated with increased incidence of T2DM.⁷⁴ In Ledergerber *et al*, 6,513 patients were followed for 6 years prospectively and it was found that indinavir demonstrated a strong association with the risk of T2DM.¹⁰⁰ In a cohorts study of 221 HIV infected patients who were followed for 5 years, Tsiodras *et al* show that the use of PIs is associated independently to elevated glucose and triglyceride levels.¹⁰² In another study, Hughes *et al* followed a cohort of 496 HIV patients in Canada for 6 years and found that the use of PIs was significantly associated with the development of diabetes.¹⁰³ Justman *et al* compared the use of PIs with RTIs in a cohort of 1,785 non-pregnant HIV positive women who were followed for four years in California. The study concluded that patients on PIs have a threefold increase in incidences of diabetes compared to RTI users.¹⁰⁴

Furthermore, when PI users were compared with PI naïve HIV patients, the result persisted in Carr *et al*. who reported that hyperlipidemia and impaired glucose were significantly common among PI users compare to PI-naïve HIV patients when followed-up at the end of 2 years.¹⁰⁵ Moreover, in a prospective cohort of 231 HIV patients that were followed for over 3 months, Calza *et al*. reported that the use of PI-based cARTs are associated with elevated serum triglycerides. Ritonavir or lopinavir/ritonavir, specifically, were found to be predictors of an increase in serum triglyceride levels.¹⁰⁶

The effects of PI were further examined using insulin resistance to measure outcomes in a cohort study of 41 patients followed for 4 months by Mulligan *et al* and his colleagues. They reported that in patients treated with PI therapy, insulin levels doubled. Additionally, fasting glucose and triglyceride levels also increased significantly.¹⁰⁷

Moreover, in a cohort study of 235 patients, those switching from lopinavir/ritonavir to an atazanavir based ritonavir-boosted (ATV/r) or an un-boosted regimen after an initial 48 weeks, had a significant decrease in mean glucose levels and insulin resistance.¹¹¹ This study suggests that patients who have achieved initial viral suppression while on lopinavir/ritonavir + two NRTIs can switch to atazanavir + two NRTIs to ensure recovery and improvement in both lipid and glycemic metabolism.¹¹¹ These studies further buttress the relationship between lopinavir/ritonavir based medication and glycemic metabolic syndrome or diabetes. Furthermore, Tripathi *et al.* utilized a marginal structural modeling approach to compare incidence of diabetes in HIV patients on HAART and their matched seronegative counterparts. They found that cumulative exposure to protease inhibitors are significantly associated with a higher risk of diabetes.¹⁰⁸

The association between PIs use and development of diabetes is stronger in the presence major confounders and strong risk factors for diabetes such as Hepatitis C Virus (HCV) infection and increasing age. In a cohort study of 1,230 HIV patients, both the HCV infection and the use PI were independently associated with an increased risk of diabetes. Additionally, the risk of developing diabetes was highest among PI users with the HCV co-infection.¹¹² In a 3 year retrospective cohort study of 101 patients Salehian *et al.* found that the likelihood of developing diabetes among protease inhibitor users increased with age and may also have a racial disparity.¹⁰⁹

In a randomized controlled trial that examined the effect of ARTs on the risk of developing diabetes, Woerle *et al.* evaluated beta-cell function, glucose production, glucose disposal and free fatty acid turnover in 13 HIV infected volunteers exposed to a protease inhibitor based cART as well as 14 healthy volunteers monitored over 12 weeks.

The results showed that exposure to a protease inhibitor based cART was significantly associated with impaired glucose tolerance.¹¹⁰

Conversely, several cohort studies have reported contradicting results. Table 2.2 summarizes some characteristics of studies that report contradicting results. In a longitudinal cohort study of 1,748 HIV-infected Thai patients followed for 9 years by Opas *et al.*, univariate cox proportional regression showed that use of protease inhibitors such as Lopinavir/ritonavir, Atazanavir/ritonavir and indinavir were not significantly associated with the risk of developing T2DM.¹¹³ In an observational, prospective, multicenter study of 1,594 HIV positive patients, Riyaten *et al.* reported that, based on a multivariate cox proportional hazard model, the use of protease inhibitors such as ritonavir, combination of nevirapine, emtricitabine combination and ritonavir-boosted indinavir, as well as combination of zidovudine, lamivudine and ritonavir-boosted indinavir were not associated with the risk of T2DM development in the patients.¹¹⁴ According to Squillace *et al.*, lopinavir/ritonavir, fosamprenavir/ritonavir, indinavir/ritonavir, saquinavir/ritonavir were not significantly associated with the risk of developing T2DM in a retrospective cohort study that included 3,546 participants.¹⁰¹

Table 2.2 Characteristics of studies that did not detect an association between use of PIs and T2DM

Author (Years)	Study title	Data source	Study design	Sample size	Treatment	Outcomes	Results
Opas (2017) ¹¹³	New-onset diabetes in HIV-treated adults: predictors, long-term renal and cardiovascular outcomes	Bangkok, Thailand HIV clinic	Cohort	1948	ARTs	Type 2 diabetes	PI use is not significantly associated with diabetes
Tien (2007) ¹¹⁵	Antiretroviral therapy exposure and incidence of diabetes mellitus in the Women's Interagency HIV Study.	Women's Interagency HIV Study	Cohort	2088	ART	Type 2 diabetes	Exposure to PI was associated with diabetes incidence in adjusted analyses
Ryaten (2015) ¹¹⁴	New-Onset Diabetes and Antiretroviral Treatments in HIV-Infected Adults in Thailand	50 public hospitals throughout Thailand (NCT00433030)	Cohort	1594	PIs and NRTIs	Type 2 diabetes	ritonavir and indinavir plus ritonavir combination were not significantly associated with onset of diabetes
Squillace (2016) ¹⁰¹	Triglyceride/HDL ratio and its impact on the risk of diabetes mellitus development during ART	Icona Foundation study	Cohort	3546	PIs and other ARTs	Type 2 diabetes	PI (atazanavir/ritonavir) is associated with DM (1.30; CI 95 % 7.98)

Abraham (2015) ¹¹⁶	Changes in blood pressure, glucose levels, insulin secretion and anthropometry after long term exposure to antiretroviral therapy in South African women	Black South African women with HIV	Cohort	103	ARTs	Type 2 diabetes	Lopinavir not significantly associated with diabetes
Butt (2009) ¹¹⁷	HIV infection and the risk of diabetes mellitus	Veterans Aging Cohort Study	Cohort	3227	ARTs	Type 2 diabetes	PI is not a significant predictor of diabetes 0.99 (0.94-1.04)
Almeida (2009) ¹¹⁸	Metabolic changes associated with antiretroviral therapy in HIV-positive patients	City of Porto Alegre (Southern Brazil)	Cohort	110	HAART	Type 2 diabetes	PI regimen is not significantly associated with changes in glucose and triglyceride levels (p=0.741)

Wand (2007) ¹¹⁹	Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection	Trial International Coordinating Committee (INITIO)	Cohort	881	ART	Fasting blood glucose	PI and PI regimen is not significantly associated with diabetes.
Gomes (2016) ¹²⁰	Incidence of diabetes mellitus and obesity and the overlap of comorbidities in HIV+ Hispanics initiating antiretroviral therapy	Dominican HIV Cohort	Cohort	153	ART	Fasting blood glucose	PI is not significantly associated with risk of impaired glucose or diabetes
Rasmussen (2012) ¹²¹	Risk of diabetes mellitus in persons with and without HIV: a Danish nationwide population-based cohort study	Danish HIV Cohort Study	Cohort	4984	HAART	Diabetes	Atazanavir and ritonavir is not significantly associated with risk of diabetes

De Wit (2008) ¹²²	Incidence and Risk Factors for New-Onset Diabetes in HIV-Infected Patients	Data Collection on Adverse Events of Anti-HIV Drugs (D.A.D)	Cohort	33,389	cART	Diabetes	exposure to ritonavir were associated with <i>decreased</i> risk of diabetes- 0.94 (0.89–0.99)
Spangnuolo (2017) ¹²³	Associations of statins and antiretroviral drugs with the onset of type 2 diabetes among HIV-1-infected patients	San Raffaele Scientific Institute (Milan, Italy)	Cohort	6,195	ART	Type 2 diabetes	HIV patients treated with atazanavir or darunavir were less likely to develop diabetes
De Wit (2008) ¹²²	Incidence and Risk Factors for New-Onset Diabetes in HIV-Infected Patients	Data Collection on Adverse Events of Anti-HIV Drugs (D.A.D)	Cohort	33,389	cART	Diabetes	exposure to ritonavir were associated with <i>decreased</i> risk of diabetes- 0.94 (0.89–0.99)

Spangnuolo (2017) ¹²³	Associations of statins and antiretroviral drugs with the onset of type 2 diabetes among HIV-1-infected patients	San Raffaele Scientific Institute (Milan, Italy)	Cohort	6,195	ART	Type 2 diabetes	HIV patients treated with atazanavir or darunavir were less likely to develop diabetes
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Furthermore, in the ‘Women’s Interagency HIV Study (WIHS), which is a multicenter prospective cohort study, Tien *et al.* compared 1,524 HIV infected women who were on a protease inhibitor based HAART to those not on a protease inhibitor based HAART, and 564 seronegative women, show that there is no significant difference in the incidence of diabetes between the groups after a 1 year follow-up period.¹¹⁵

In Abraham *et al.*, use of PI- Lopinavir was not associated with the risk of developing T2DM.¹¹⁶ In Butt *et al.*, multivariate result of the 3,327 HIV-infected and 3,240 HIV-uninfected subjects show that protease inhibitors are not a predictor of diabetes after adjusting for other covariates.¹¹⁷ Almeida *et al.* did not detect a significant association between the use of protease inhibitors and the risk of diabetes.¹¹⁸ Also, Wand *et al.* compared the use of NNRTI with a combination of PI + NNRTI, and PI only in a cohort study and reported that neither the use of PI + NNRTI, PI, or NNRTI were significant predictors of diabetes.¹¹⁹ Similarly, long term exposure to protease inhibitors was not found to be a significant predictor of diabetes in a large multicentered Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort study of 32,437 patients followed over a 6 year period.¹²² In patients receiving protease inhibitors containing cART regimen, Gomes *et al.*, found that the use of a regimen containing a protease inhibitor is not significantly associated with the risk of impaired glucose or diabetes.¹²⁰ This result persists in Rasmussen *et al.*, which reported that the use of protease inhibitors such as indinavir, nelfinavir, atazanavir, ritonavir +/-lopinavir are not significantly associated with the risk of diabetes among HIV positive patients in Denmark.¹²¹

Furthermore, several studies reported that use of a protease inhibitor confers a protective effect from the risk of diabetes among patients with HIV/AIDS. In Tien *et al.*, exposure to ritonavir and nevirapine were both associated with a reduced risk of diabetes.¹¹⁵ Similarly, De Wit *et al.* concluded that exposure to ritonavir was associated with a decreased risk of diabetes.¹²² Furthermore, in another cohort study of 6,195 HIV patients, Spangnuolo *et al.* reported that HIV patients treated with atazanavir or darunavir were less likely to develop diabetes.¹²³

2.2 Race/ethnicity Disparity in PI use and Development of T2DM

Racial variation in the prevalence of HIV/AIDS is well documented in the literature with the highest prevalence reported among African Americans.¹²⁴ Nearly half of all HIV/AIDS incidents occur among African Americans with a prevalence rate 8 times higher than in Caucasians.¹²⁴ African-Americans are also shown to have poorer HIV infection prognoses and death rates that are 9 times higher than those of Caucasians.¹²⁵⁻¹²⁷ Several studies suggest that this racial disparity in health indices is a function of various factors related to demography, socio-economy, access to quality healthcare, individual habits, as well as attitudes and level of trust in the healthcare system.¹²⁵⁻¹²⁷

Even though access to HIV care is critical for the survival of HIV/AIDS patients, access to ARTs and HIV treatment is not equitably distributed among HIV/AIDS patients in the US. Gebo and his colleagues examined racial disparity in receipt of HAART in 2001 and found that racial disparities do exist.⁵ Furthermore, Fleishman *et al.* concluded that being a younger African American female is associated with lower receipt of ART.¹²⁸ Palacio and his colleagues reviewed the literature and concluded that, based on

available evidence, HIV positive minorities have lower ART use compared to HIV infected Caucasians.¹²⁹ Despite Medicaid's potential for equitable access to care through equity in insurance coverage for all enrollees, there is evidence that racial/ethnic disparity in receipt of HAART exists between both Medicaid beneficiaries enrolled in Fee-For-Services and managed care¹³⁰⁻¹³².

Given evidence of racial disparity in HIV/AIDS treatment, potential disparity in HIV/AIDS treatment outcomes and adverse events such as the risk of diabetes may exist. An effective risk management in the clinical use of ART would require proper consideration of how the risk of diabetes following the use of ART varies among HIV infected patients of different ethnicities. Based on the literature review, no studies have examined possible racial/ethnic disparity in the development of diabetes following PI based treatment among HIV infected Medicare recipients. To fill this knowledge gap, we therefore seek to examine the racial disparity in the development of diabetes among HIV positive Medicare patients who are on PI.

2.3 Economic Burden of Comorbid T2DM

Improvement in the methods of HIV detection, early diagnosis, and treatment with ARTs has resulted in improvement in patient's survival and, consequently, a steady growth in the population of HIV survivors.¹³³ Access to potent ARTs reduce morbidity and mortality which increases the life expectancy among patients with HIV/AIDS. Consequently, the number of elderly patients with HIV/AIDS increases proportionately. HIV/AIDS infected patients over the age of 65 are predisposed to age-related chronic complications in addition to treatment-related adverse events.⁶⁸ Comorbidities with

HIV/AIDS among the elderly not only constitute challenges in clinical management but may also cause a major economic burden for patients and insurers.

HIV/AIDS and ART-associated diabetes and other metabolic syndromes are commonly encountered in clinical management of HIV/AIDS and is most likely to occur as treated patients grow older.⁶ Comorbidities with HIV/AIDS may pose significant clinical challenges as well as an economic burden on the US Medicare system given the increasing number of surviving elderly with HIV/AIDS- the population demographic that is most predisposed to diabetes and other age related chronic conditions.⁷ Studies show that 83% of elderly HIV patients had at least one comorbidity compared to 69% in elderly non-HIV patients and 63% in younger HIV patients.¹³⁴ A longitudinal study of Medicare beneficiaries reports that the prevalence of diabetes in elderly patients with HIV is 19.4% and 27.3% (hyperlipidemia).¹³⁵ In Taiwan, the prevalence of diabetes among men and women 60 years old and above are 21% and 16.7% respectively.¹³⁶

Economic burden due to diabetes comorbidity among HIV/AIDS patients has been reported. Among HIV positive Medicare beneficiaries enrolled in California Medicare, the mean per capital expenditure for HIV/AIDS patients with complicated and uncomplicated diabetes is as high as \$92,992 and \$66,275 respectively per annum.⁷

Although, the prevalence and expenditure of diabetes comorbidity in California is known, the current national economic burden of diabetes comorbidities among HIV positive Medicare beneficiaries is not known. As clinical management of HIV/AIDS is progressively expanding to include chronic and metabolic complications as well as treatment-related adverse effects, this study seeks to specifically explore the national economic burden of diabetes comorbidity in terms of total OOP cost to the patients, total

prescription cost, total Medicare cost, total inpatient cost, total outpatient cost and overall total healthcare costs. Understanding the economic burden of diabetes comorbidity on the Medicare system and individual patients could motivate the development of policy and regulatory strategies that drive efficient resource allocation to contain the additional economic burden on patients and the Medicare system.

2.4 Literature Gaps

Based on the review of literature, the following literature gaps were identified and have informed the objectives of this study.

- ✧ Evidence of an association between PIs use and the development of T2DM has been largely debated in research across the world. Given the available inconclusive and controversial evidence, more research is needed to support or refute currently available evidence in order to draw conclusions.
- ✧ To date, no study has explored this association among Medicare beneficiaries. Thus, evidence of PIs use and the odds of developing diabetes among the Medicare population with HIV/AIDS is unknown.
- ✧ To date, no study has examined possible racial/ethnic disparity in the development of diabetes following treatment with PI among HIV infected Medicare beneficiaries.
- ✧ To date, no study has evaluated the national economic burden of comorbid diabetes among Medicare beneficiaries living with HIV/AIDS.

2.5 Study Objectives and Specific Aims

The objectives of this project were to (1) examine the association between treatment with PIs and the risk of developing T2DM among Medicare beneficiaries living with HIV/AIDS, (2) assess racial/ethnic disparity in odds of developing T2DM among HIV/AIDS positive beneficiaries treated with PI and (3) to determine the economic burden of comorbid T2DM among Medicare beneficiaries living with HIV/AIDS

2.5.1 Aim 1: Treatment with PI and development of T2DM

Aim 1: To assess the association between treatment with PIs and development of T2DM among Medicare beneficiaries with HIV/AIDS.

Use of PI has been associated with the risk of metabolic syndrome which includes development of T2DM among patients with HIV/AIDS. While this evidence is currently being debated globally, evidence among the Medicare population is yet to be reported. We, therefore, hypothesize an increased odds of developing T2DM among Medicare HIV/AIDS positive beneficiaries treated with PIs compare to those treated with non-PIs and those who had no-ARTs.

Hypothesis 1.1: We hypothesize that HIV/AIDS positive Medicare beneficiaries treated with PIs are more likely to develop T2DM compared to HIV/AIDS positive beneficiaries treated with non-PIs.

Hypothesis 1.2: We hypothesize that HIV/AIDS positive Medicare beneficiaries treated with PIs are more likely to develop T2DM compared to HIV/AIDS positive beneficiaries who had no-ARTs.

2.5.2 Aim 2: Racial disparity in development of T2DM following treatment with PI

Aim 2: To examine racial/ethnic disparities in development of T2DM following treatment with PIs among Medicare beneficiaries with HIV/AIDS.

Racial disparity in the epidemiology of HIV infection and treatment have been reported. As a result, racial disparity in development of T2DM following treatment with PIs may exist. We, therefore, hypothesized that the odds of developing T2DM following PI use may vary among Caucasian and African American HIV/AIDS positive Medicare beneficiaries.

Hypothesis 2.1: Comparing PIs versus non-PIs therapy group, we hypothesize that the odds of developing T2DM following treatment with PIs is higher among African American race compared to the odds of developing T2DM after treatment with PI among the Caucasian beneficiaries.

Hypothesis 2.2: Comparing PIs versus no-ART therapy group, we hypothesize that the odds of developing T2DM after treatment with PIs is higher among the African American race compared to the odds of developing diabetes after treatment with PI use among the Caucasian beneficiaries.

2.5.3 Aim 3: Economic burden of comorbid T2DM in beneficiaries with HIV/AIDS

Aim 3.1: To assess the incremental healthcare cost associated with comorbid T2DM among beneficiaries with HIV/AIDS

Although the economic burden of diabetes comorbidity in California Medicare is known, the current national economic burden of comorbid T2DM among HIV/AIDS positive

Medicare beneficiaries is unknown. We, therefore, hypothesize that total medical cost, total prescription cost, hospitalization cost, outpatient cost, total Medicare and OOP cost will increase for Medicare beneficiaries with comorbid T2DM compared to those without comorbid T2DM.

Hypothesis 3.1: In HIV/AIDS positive Medicare beneficiaries with comorbid T2DM, total medical costs are higher compared to HIV/AIDS positive beneficiaries without comorbid T2DM

Hypothesis 3.2: In HIV/AIDS positive Medicare beneficiaries with comorbid T2DM, total Medicare expenditures are higher compared to HIV/AIDS positive beneficiaries without T2DM

Hypothesis 3.3: In HIV/AIDS positive Medicare beneficiaries with comorbid T2DM, total cost of hospitalization is higher compared to HIV/AIDS positive beneficiaries without comorbid T2DM

Hypothesis 3.4: In HIV/AIDS positive Medicare beneficiaries with comorbid T2DM, total outpatient cost is higher compared to HIV/AIDS positive beneficiaries without comorbid T2DM

Hypothesis 3.5: In HIV/AIDS positive Medicare beneficiaries with comorbid T2DM, total OOP cost is higher compared to HIV/AIDS positive beneficiaries without comorbid T2DM.

CHAPTER 3

CONCEPTUAL FRAMEWORK

This chapter presents the conceptual framework based on Andersen's behavioral model of health services, which was used to emphasize contextual and individual determinants of access to care. This chapter also presents discussions on how the Andersen's model is adapted in this study to conceptualize the relationships between treatment with PIs and T2DM, racial/ethnic variation in risk and the economic burden of diabetes among individuals with HIV/AIDS.

3.1 Andersen's Behavioral Model

Andersen's behavioral model of health service utilization was first developed in the late 1960's and has undergone several modifications over the years.¹³⁷ This model is based on contextual and individual determinants of access to healthcare. Contextual determinants consist of the environment and circumstances impacting on health care access. Contextual determinants are aggregate level determinants ranging from small units (family, work group) to large units (country, community) unlike the individual determinants. The model suggests that each of the contextual and individual determinants constitute three major components of determinants which include: (1) predisposing factors that impacts health care access, (2) enabling factors that can facilitate or prevent the use of available health care and, (3) healthcare needs and other related conditions that inform healthcare use.¹³⁷

3.1.1 Individual characteristics domain

Predisposing characteristics at the individual level include age, gender, weight, height and genetic factors which may predict health care needs and predisposition to certain healthcare conditions which could motivate health care needs.¹³⁸ Common chronic disease conditions such as T2DM cardiovascular diseases, age-related macular degeneration, depression, and cancer are not only age related and linked to family history but also has multifactorial and polygenetic etiology.¹³⁹ Social factors consist of factors related to an individual's status in the community and his/her ability to cope with immediate challenges and financial demands to addressing these challenges. These factors may include individual's education level, race and ethnicity as well as occupation. Social factors may also include units of a society such as the family and friends as well as religious and social organizations that helps by improving societal cohesion and the social support needed to improve access to health care services.¹⁴⁰ Furthermore, culture and belief systems could impact the individual's perception of illness and treatment approaches.¹⁴¹ Belief systems may greatly impact their perception of needs for health care as well as use of health care services.¹⁴¹

Enabling factors to accessing health care ranges from having the resources to pay for healthcare services, presence of affordable health insurance in terms of effective prices for services, low cost sharing amount and deductibles. Social support from social organizations, religious organizations and social networks could be considered enabling factors from the perspective of emotional support, informational and affectionate support, and in some cases, financial support to obtain healthcare services.¹⁴² The need for health care, in general, is a function of both the patient's perceived healthcare needs and

evaluated health care needs, which are based on objective, professional medical judgment. Professional judgment stems from the state of the art and sciences of medical practice, clinical guidelines and protocols, practice patterns, training, and competency of professional experts.¹⁴⁰ These constitute individual characteristics factors as shown in Figure 3.1.

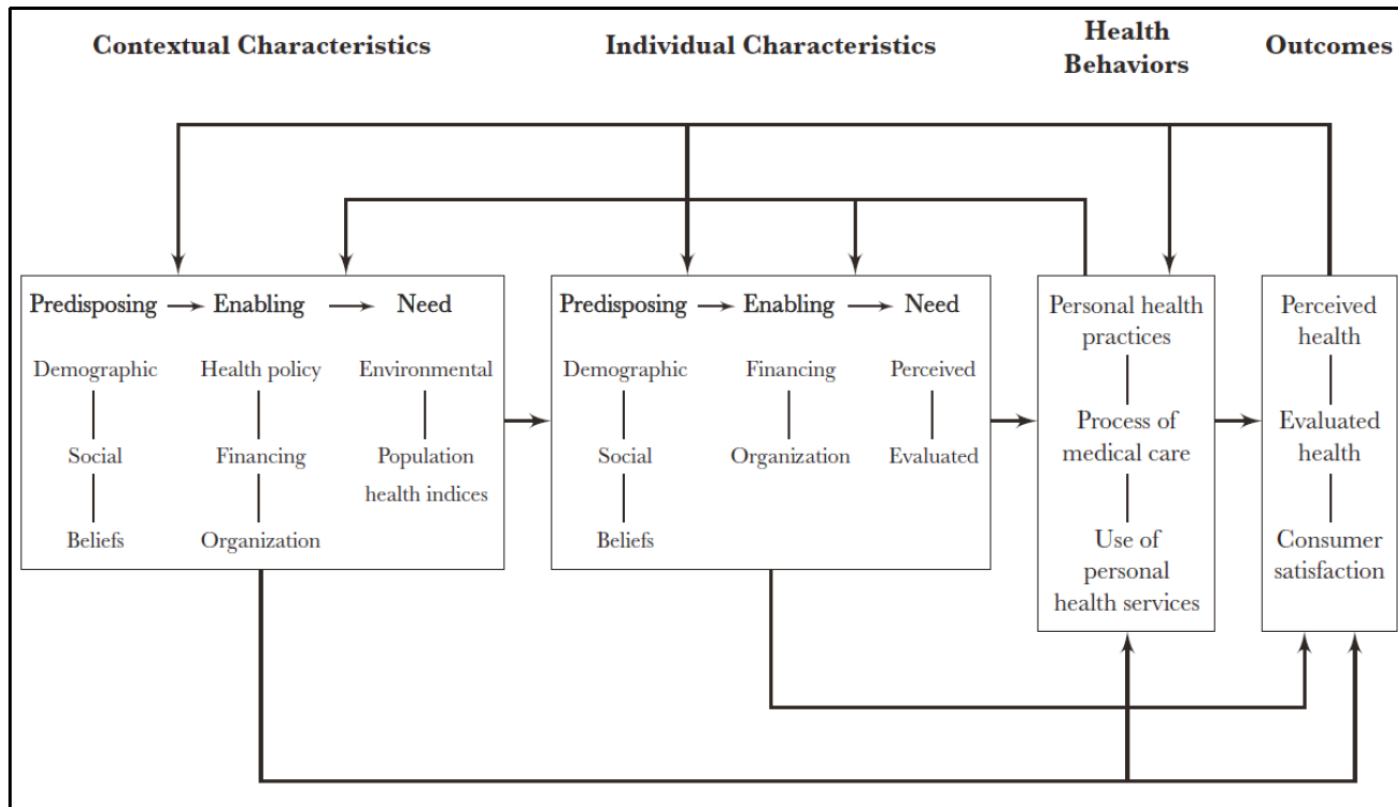


Figure 3.1: The Andersen's behavioral model

Source: Andersen RM, Davidson PL, Baumeister SE. Improving access to care in America. Changing the US health care system: key issues in health services policy and management 3a edición San Francisco: Jossey-Bass. 2007:3-31.

3.1.2 Contextual characteristics domain

Collective individual demographic characteristics such as being elderly, married, female or male defines context characteristics and explains the way in which these characteristics may influence the availability of certain health care services when compared to a setting with a younger, single population.¹⁴⁰ Social support at this level constitutes community or county-based support because it is available in the community where people live. This kind of support may have an impact on the local population's health and access to care. Additional context predisposing characteristics may include spatial segregation and distribution of race and ethnicity within certain populations, educated versus uneducated people groups, employment rate and crime rates within a community.¹⁴³ Common and diverse belief systems, culture, political ideologies and prevailing organizational values underpin the organization of healthcare, as well as how it is financed and made available to the community members.¹⁴⁰

The major enabling factors in the context of characteristics or population-based factors that impact access to care consist largely of governmental (legislative, executive or judicial) public health policies designed to enable aggregate access to health care for the community or for a relevant community sub-group.¹⁴⁰ The Affordable Care Act (ACA) represents a good example of a legislative public health policy which impacts access to care from the local to the national level. Other policies may include private and internal organizational policies that may enable access to aggregate care. Some may include managed care organization policies concerning product pricing, marketing or product lines and quality assessment policies from the National Committee for Quality Assurance (NCQA).¹⁴⁰ From the perspective of contextual enabling factors, financial policies, in

addition to health policies ,represent available resources to pay for health care. Those policies also consider the communities' per capita income and wealth and incentives for payment of health care services. In addition they consider provider's methods of compensation that would sustain a reasonable cost of health care and health insurance coverage in the community.¹⁴⁰ Availability and distribution of health facilities, providers/personnel ratio to patients, physician and hospital bed ratios and the way in which the facilities are structured for healthcare delivery represents organizational enabling factors that impact on access to care in the community.

Need characteristics in the context perspective constitutes the environment where people live and how it predicts their perceived or evaluated health needs. The model suggests that physical environment, such as quality of housing, water, and air, could suggest how healthy the environment might be and the prevailing health needs.¹⁴⁰ Death and injury rates as well as environmental causative factors could also suggest the community health status and aggregate health care needs.¹⁴⁰ High mortality or morbidity rates may be linked to specific environmental factor such as road accidents, disease epidemics, infant mortality and a high prevalence of chronic conditions. These individual and context characteristics typically influence health behavior and the prevailing health outcomes.

3.1.3 Health behaviors

Health behaviors are those health-related activities and habits that individuals exhibit towards their health care. They may include healthy living such as diet and nutrition, exercise, alcohol and drug abuse, health consciousness and adherence to medical advice and medication use or non-compliance. Good health behavior is a

function of how well the provider interacts with a patient during the care process.

According to Donabedian, the process of medical care constitutes an effective interaction between the provider and the patient that would lead to the patient exhibiting essential behavior and habits that will benefit their health. This includes adherence to care, compliance with medications, and dieting.¹⁴⁴ A quality care process could be determined by measures such as patient and physician communication, provider counselling and education, prescription patterns, ordering of necessary diagnostic tests, and relevant vital signs examinations. Personal health service use is an essential component of healthy behavior. Based on the model, the contextual predisposition, enabling, and need factors occurring through the individual characteristics predicts health services use.¹⁴⁰ The use of health services may occur as inpatient care, outpatient care, dental care or ambulatory. The type of care is determined by predisposing factors such as age, gender, genetic dispositions, enabling factors such as availability of facilities, insurance and financial resources to afford care and finally the perceived and evaluated healthcare need such as pain, diagnosis and laboratory results. For instance, a patients perceived need for dental care may result from a tooth ache, pain, bleeding gums, social conditions, health beliefs, and/or enabling resources.¹⁴⁰ The severity of condition of the patient's health based on evaluated need would predict more intensive care at the inpatient level rather than less intensive care at the outpatient level.

The Andersen's behavioral model suggest that contextual characteristics can influence health behaviors and outcomes in multiple ways through individual characteristics.¹⁴⁰

For instance, the Medicaid expansion policy leads to increased insurance rates for low-income children and members of society, thereby resulting in increased health services use.

3.1.4 Outcomes

Patients' health behavior, personal health services, individual characteristics, and global context environment influence their health outcome or perceived health status. Based on this model, the purpose of personal healthcare use is to reduce the perceived or evaluated health care needs which is measured as health status improvement from the patient's perspective and the physician's evaluated perspective.¹⁴⁰ A patient's perceived health outcomes may include lack of pain after treatment, improvement in daily functionality, and improved general well-being. Comparatively, evaluated health status includes laboratory test results and analysis of biomarkers of disease prognosis. The patient's perceived outcomes can also be measured as their satisfaction of the health care services, they received, which could be measured in terms of a patient's rating of the provider on patient communication, waiting time, hospitalization days, and frequency of re-admissions. Whether or a not a patient switches care plans could also be used as a measure for satisfaction from the health insurance perspectives.¹⁴⁵

With the increasing need and interest in patient-centered care, Patient Reported Outcomes (PRO) is increasingly being used to measure overall treatment benefits from the perspective of the patient. Typically, PROs are used for the purpose of documenting patient experiences with treatment in terms of side effects, the improvement of symptoms, and quality of life.¹⁴⁶ Thus, incorporating quality of life in the Andersen's behavioral model would better explain a patient's perceived reduction in quality of life

related to their healthcare needs.¹⁴⁰ Quality of life measures is one of the seven constructs used in patient reported outcome instruments (PRO) and it is the most frequently used of the PRO measurement constructs. Several PRO tools are constructs such as Functional Assessment of Cancer Therapy—Breast (FACT-B), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30, EuroQol 5-Dimensions and EORTC QLQ—Breast Cancer Module.¹⁴⁶

3.2 Adapted Model

This model is applied in this dissertation to explain the association between use of PIs and the odds of developing T2DM among HIV positive Medicare beneficiaries continuously enrolled in Medicare Part A, Part B and Part D, to explain racial variations in the development of T2DM, and additional costs of healthcare use due to comorbid T2DM. Figure 3.2 represents the conceptual framework adapted from Andersen's behavioral model for this dissertation. The adapted model consists of the individual and contextual characteristics and outcomes.

Environmental or regional factors are important predisposing factors to certain disease conditions which predict regional healthcare use and health outcomes. For instance, regional disparity in the prevalence of T2DM can be seen in that it is disproportionately distributed in the Southern regions of the US, also referred to as the 'diabetes belt'.¹⁴⁷ Regional disparities in T2DM prevalence is a function of disproportionate distribution of risk factors of T2DM, infrastructures and facilities that enable a healthy life-style.¹⁴⁷ A recent study suggested that community-level correlates of T2DM prevalence were significantly different between the 'diabetes belt' and other US regions.¹⁴⁸

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 which established the Medicare Part D prescription drug program on January 1, 2006 represents context based enabling factors through the Low-Income Subsidy (LIS) program, which is offered to Medicare beneficiaries. With this legislative Act, beneficiaries can access expensive HIV/AIDS medication through Medicare Part D and additional cost sharing assistance for those eligible for LIS.

Individual predisposing characteristics include demographic factors such as age and gender which are known to be associated with health care use. Race/ethnicity is a relevant social factor because of its association with T2DM and HIV/AIDS, and thus predicts access to care and health outcomes for individuals with these conditions. The epidemiology of T2DM and HIV/AIDS varies across race/ethnicity among Medicare beneficiaries.^{12,65} Individual enabling factors is constituted of their enrollment in Medicare Part A and Part B insurance plans and dual eligibility in both Medicare and Medicaid which impacts health care use. Another individual enabling factors for health care access include enrollment in both Medicare and Medicaid, otherwise known as dual eligibility. Dual eligible beneficiaries receive extended and more comprehensive coverage with cost sharing assistance since Medicaid covers services which Medicare does not cover and vice versa. Also, Medicaid provides supplemental coverage that helps to cover premiums and cost sharing for low-income dual beneficiaries.⁴⁹ Individual need for healthcare is constituted of the patient's perceived symptoms and evaluated need for HIV/AIDS and diabetes treatment based on diagnostic tests and clinical assessment.

In the adapted model, Medicare beneficiaries diagnosed of HIV/AIDS or diabetes are either hospitalized or treated on an outpatient basis and receives medication through

Medicare Part D. The health behavior domain also includes study outcomes, which in this dissertation is the diagnosis of diabetes following treatment with PIs as an adverse drug event. This dissertation aims to determine the odds of developing T2DM among HIV/AIDS patients treated with PIs compare to those treated with other medications. Based on the physiological process of HIV treatment and the risk of diabetes, use of PIs is associated with T2DM through impact on insulin sensitivity, resulting in insulin resistance, and consequently T2DM. Secondary outcomes in the adapted models include race/ethnicity variation in the development of T2DM and a measure of additional cost of care due to T2DM comorbidities among beneficiaries with HIV/AIDS. The presence of diabetes among HIV/AIDS positive Medicare beneficiaries may constitute additional healthcare utilization and a corresponding incremental economic burden to Medicare, patients, and the entire US healthcare system.

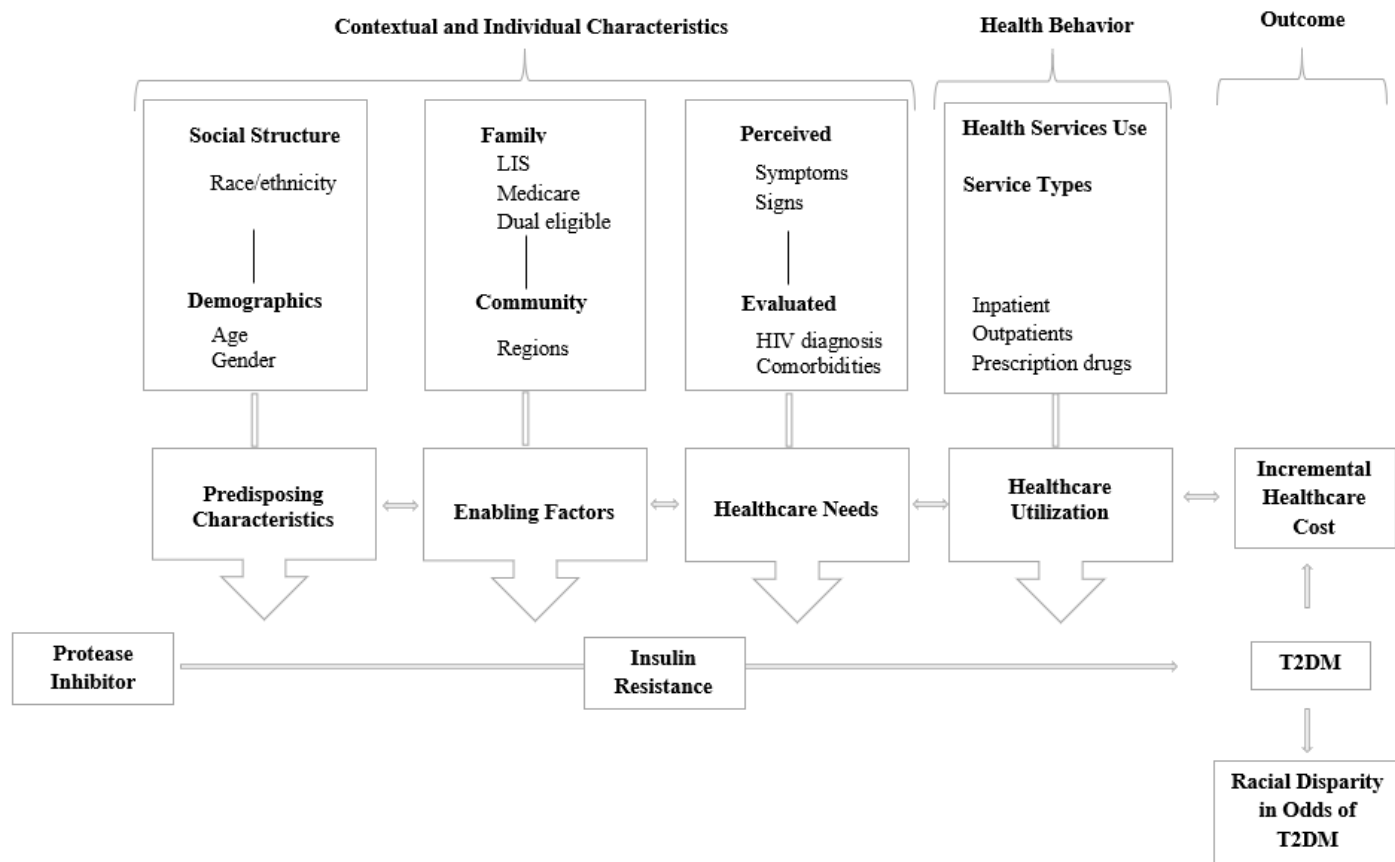


Figure 3.2: Adapted Andersen's Behavioral Model

CHAPTER 4

RESEARCH METHOD

This section discussed various aspects of research methodology including data sources, the study design, the study population, definition of case and control groups, variables, and statistical analysis.

4.1 Data Source

A random sample of national Medicare administrative claims data from the years 2013 to 2017 was used to analyze Medicare population with HIV/AIDS. Medicare is the US federal health insurance program established in 1965 to provide healthcare coverage for Americans aged 65 years or older, regardless of income level or medical history.⁵⁰ Medicare coverage was expanded in 1972 to provide coverage for individuals under 65 years of age with long-term disability and who receive Social Security or Railroad Retirement Board benefits, and individuals with End Stage Renal Disease.^{50,149} Currently, Medicare provides health coverage to 60 million people who are disabled or elderly. This coverages provides basic health services such as inpatient care, physician visits, prescription drugs, preventive services, skilled nursing facilities, home health care, and hospice care.⁵⁰ Approximately 84 % of beneficiaries are eligible for Medicare benefits because of age, while 16 % are younger beneficiaries who receive benefits because of disabilities such as end-stage renal failure.¹²

Medicare health insurance constitutes Part A (hospital insurance), Part B (medical insurance), Part C (Medicare Advantage) and Part D coverage types. Parts A, B, and D are available through traditional Medicare Fee-For-Service (FFS) plans. Part A insurance type is a plan that provides coverage for care received in inpatient settings, SNF, hospices, or home health care settings. Part B, also known as medical insurance, covers physician services such as injections, procedures, diagnostic tests, other outpatient care, DMEs, preventive services, and some home health care regardless of whether care was received in an inpatient or outpatient setting. Almost all Medicare beneficiaries are enrolled in either of Part A, Part B, or both.¹⁵⁰ In 2006, Medicare offered Part D, prescription drug coverage, to eligible beneficiaries. Beneficiaries enrolled in the Part D plan receive benefits that help pay for outpatient prescription drug costs, which is essential for low income patients with especially expensive drug costs.⁵⁰ Plan D coverage is voluntary and occurs through contractual arrangements between Medicare and private plans such as PDPs and MA-PDs.⁵⁰ The Part D plan also provides additional financial benefits for enrollees with low incomes and modest assets. In 2018, 25% of the over 43 million Medicare beneficiaries who were enrolled in either a PDP or MA-PD received a low-income subsidy.⁵⁰

Typically, Medicare data include enrollment information of each beneficiary, including information such as enrollment eligibility, demographic characteristics and claims information. This information captures nearly all aspect of healthcare services throughout all levels of healthcare.¹⁵¹ For services provided to Medicare beneficiaries, physicians and other healthcare providers submit claims to the Center for Medicare and Medicaid Services (CMS). The CMS then review and process the claims for

reimbursement to the healthcare providers. From the reviewed claims, the CMS generates Standard Analytical Files (SAF) annually. Typically, the SAF contains final researchers encrypted claims for Parts A and B services and Part D prescription drugs for services received in the hospital, physician offices, hospice, and SNFs through December 31 of the latest available calendar year.¹⁴⁹ SAF also contains beneficiary's enrollment and demographic information such as gender, age and race/ethnicity as well as provider characteristics such as the provider's unique number, the physician's clinical specialty, the national physician number and geographic information for facilities.¹⁴⁹ This study uses a national random sample of 1 million Medicare beneficiaries. It is suitable for this study because it covers nearly all health care utilizations for each eligible beneficiary across all levels of healthcare services provision. Specifically, it is rich in information such as demographic data, claims and costs, clinical and diagnosis information, prescription drug use and costs, all payments sources, along with mortality and discharge information.

4.2 Study Design

In study aim 1 and 2, we performed a nested case-control study of Medicare beneficiaries living with HIV/AIDS to analyze the association between treatment with PI and development of T2DM. (Figure 4.1.) In study aim 3, a pooled cross-sectional study design was used to analyze the economic burden of comorbid T2DM among beneficiaries diagnosed with HIV/AIDS for a pooled period of 2013 - 2017. The study protocol was approved by the University of South Carolina Institutional Review Board (IRB) as exempt from human subject protection review since it is an observational study with administrative claims.

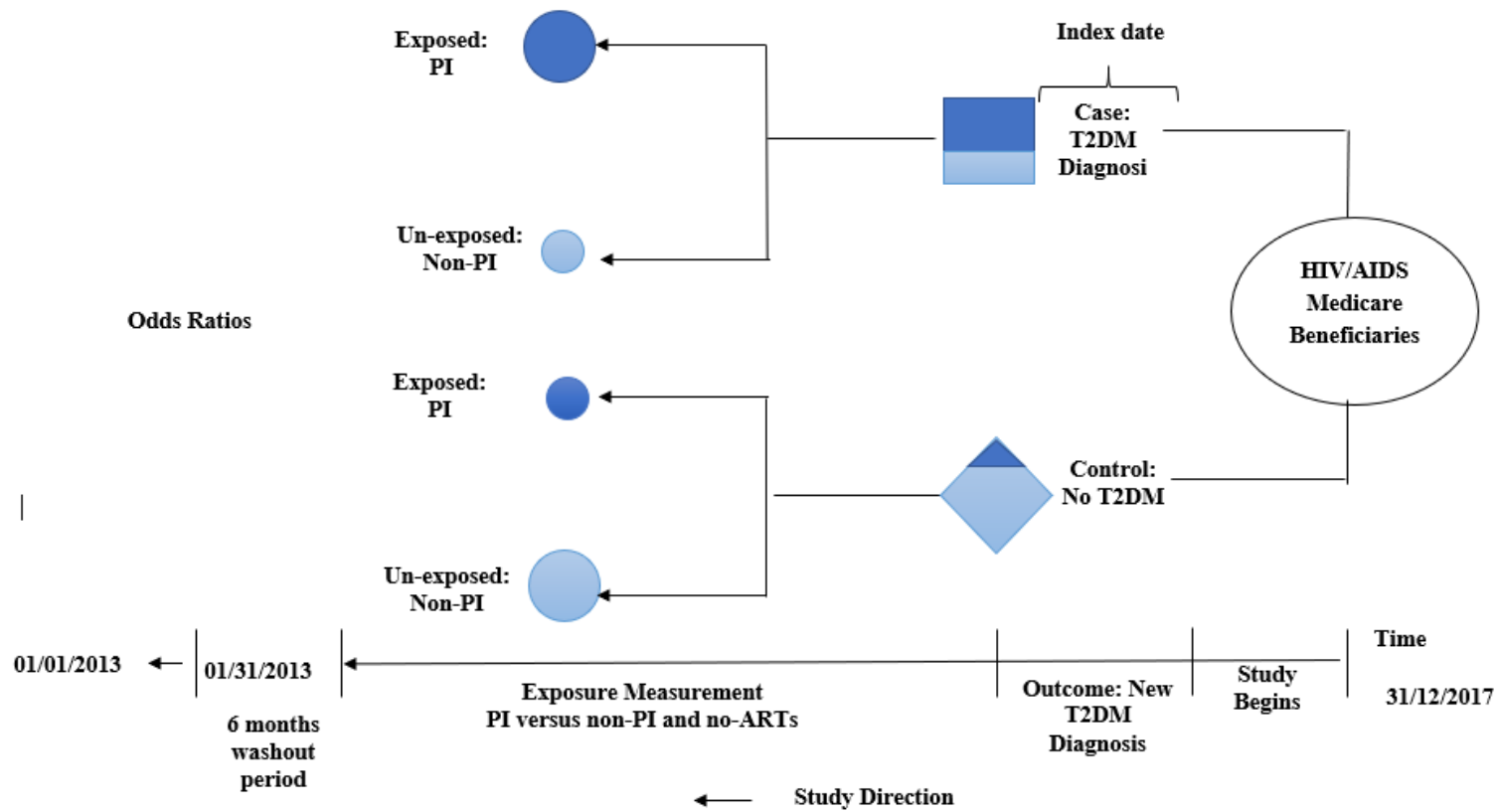


Figure 4.1: Study design sketch for study aim 1 and 2

4.3 Study Population

In study aims 1 and 2, we identified beneficiaries with diagnosis of HIV/AIDS based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code for HIV/AIDS (042-044, 079.53, V08)¹⁵² and/or International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for HIV/AIDS (B20.xx, Z21)¹⁵³ between 2013 to 2017. Six months washout period starting from January 1 to July 1, 2013 was applied to determine new T2DM diagnosis. (Figure 4.1.) The cohort entry date was set as the date after the washout period (July 1, 2013). The study included only beneficiaries that were continuously enrolled in Medicare Part A and B plans throughout the analytical time frame to ensure complete diagnosis information and medical records. Medicare beneficiaries enrolled in HMOs were also excluded.

In study aim 3, the study sample includes Medicare beneficiaries who have been diagnosed with HIV/AIDS based on the ICD-9-CM code for HIV/AIDS (042-044, 079.53, V08)¹⁵² and/or ICD-10-CM code (B20.xx, Z21).¹⁵³ To ensure a complete diagnosis and medical records, only beneficiaries that were continuously enrolled in Medicare Part A and B throughout the analytical time frame were included. Medicare beneficiaries enrolled in HMOs were excluded. The study excluded Medicare beneficiaries with End Stage Renal Disease (ESRD) because healthcare expenditure for beneficiaries with disabilities such as ESRD is more than twice as much for people with persistent or chronic disabilities than for those with temporary or no disability.¹⁵⁴ Excluding these patients would help prevent extreme or outlying cost observations and its possible impact on regression estimate.

4.4 Case and Control Groups

In study aim 1 and 2, we identified cases as HIV/AIDS positive beneficiaries with diagnosis of T2DM based on the ICD-9-CM code (250.xx) or ICD-10-CM code (E11.xxx).¹⁵⁵ The first diagnosis of T2DM was set as the index date. Control group included HIV/AIDS positive beneficiaries who had no record of a T2DM diagnosis. (Figure 4.1.)

4.5 Measurements

4.5.1 Dependent and independent variables

Medication exposure variable for this study were classified into (1) PI treatment defined as cumulative treatment with PIs (≥ 60 -day supply), (2) non-PI treatment defined as cumulative treatment with PIs (≤ 60 -day supply); and or treatment with other ARTs; and; (3) no-ART treatment defined as beneficiaries with no ART prescriptions.

Measurement of PI use in this study is a modified form of measurement approach used in Tripathi *et al*¹⁰⁸ (Table 4.1). Tripathi *et al* calculated exposure to ART based on 30-day exposure while in this study, we calculated PI use based on a 60-day cumulative use.

Treatments were based on the most recent prescription date preceding the index date or December 31, 2017 whichever came first. Drug use information was extracted from the prescription drug event file component of the Medicare data using the generic name variable. Two therapy comparison groups were created from the medication exposure variables as follows: (1) cumulative treatment with PI (≥ 60 days) versus cumulative treatment (≤ 60 -day) and or treatment with other ARTs and (2) cumulative treatment with PI (≥ 60 days) versus no treatment with ART. The outcome of interest for study aims 1

and 2 was the diagnosis of T2DM determined based on ICD-9-CM code (250.xx) or ICD-10-CM code (E11.xxx).¹⁵⁵ T2DM diagnosis variable was categorized into two level binary variables- T2DM= 1 for positive diagnoses and T2DM=0 for negative T2DM diagnoses.

In study aim 3, the main predictor variable was comorbid T2DM assessed based on ICD-9-CM code (250.xx) or ICD-10-CM code (E11.xx)¹⁵⁵. The predictor variable was categorized into two level binary variable- T2DM= 1 for positive diagnoses and T2DM=0 for negative T2DM diagnoses. The outcomes measures in study aim 3 were six relevant measures of economic burden such as the costs of health care services received- (1) total hospitalization cost, (2) total outpatient cost, (3) total prescription costs, (4) total Medicare costs, (5) total OOP and (6) total medical costs. The Assessment of the economic burden based on these costs ensures availability of evidence of economic burden across all facets of health care service types -inpatient, outpatient and OOP.

The Medicare inpatient and outpatient analytical file consist of cost variables which include: 'claim payment amount', 'claim pass thru per diem amount', 'claim utilization day count', 'NCH beneficiary inpatient deductible amount', 'NCH beneficiary part a coinsurance liability amount', 'NCH beneficiary blood deductible liability amount' and 'NCH primary payer claim paid amount'.¹⁵⁶ Total Medicare cost was calculated by summing up the 'claim payment amount' and the product of the 'claim pass thru per diem amount variable' and the 'claim utilization day count variable' in the inpatient and outpatient files and calculating average annual Medicare cost per patient.¹⁵⁶ Total OOP cost was calculated by summing up the NCH beneficiary inpatient deductible amount variable, NCH beneficiary Part A coinsurance liability amount variable, and the NCH

beneficiary blood deductible liability amount variable from both the inpatient and outpatient files and calculating average annual OOP per patient.¹⁵⁶ Total inpatient costs were calculated by summing up the total Medicare inpatient payments + OOP inpatient costs + NCH primary payer claim paid amount in the inpatient file and calculating average annual inpatient cost per patient. Total outpatient cost was calculated by summing up the total Medicare outpatient costs + OOP outpatient costs + NCH primary payer claim paid amount in the outpatient file and calculating average annual cost per patient.¹⁵⁶ Total prescription drug costs were determined using the gross drug cost variable- 'TOT_RX_CST_AMT'. Total medial costs were calculated by summing the total OOP costs, total Medicare payments, and the total prescription cost and calculating average annual medical cost per patient.

Table 4.1: List of peer reviewed studies and measurement approach for ART exposure

Author (Years)	Study Title	Study Design	ART Measurement Approach
Rasmussen (2012) ¹²¹	Risk of diabetes mellitus in persons with and without HIV: a Danish nationwide population-based cohort study	Cohort Study	Patient initiated on a specific ART regimen was considered exposed to such regimen for the rest of the observation period independent of cessation or changes in antiretroviral therapy.
Neto (2013) ¹⁵⁷	Dyslipidemia and fasting glucose impairment among HIV patients three years after the first antiretroviral regimen in a Brazilian AIDS outpatient clinic	Retrospective Cohort Study	Only patients on their first ART regimen were studied. In case of change or discontinuation of initial ART regimen, ART regimen used for at least 70% of the study period was considered.
Tripathi (2015) ¹⁰⁸	Incidence of diabetes mellitus in a population-based cohort of HIV-infected and non-HIV-infected persons: the impact of clinical and therapeutic factors over time	Retrospective Cohort Study	Exposure to combination ARTs was based on 30-day cumulative use.
García-benayas (2006) ¹⁵⁸	Higher Risk of Hyperglycemia in HIV-Infected Patients Treated with Didanosine Plus Tenofovir	Retrospective Cohort Study	Exposure to ART was based on unmodified use of any ART regimen for a period of 12 month.

Estimating the economic burden based on health expenditures over the years requires an adjustment for inflation to dollars of equivalent purchasing power because costs incurred this year for instance is not the same as the costs incurred over the previous years for the same items or services received. Prices for health care changes annually and faster than overall price inflation. Thus, selecting indexes that are specific for medical

expenditures and also account for changes in healthcare prices is paramount for correctly estimating health care expenditure.¹⁵⁹

Consequently, the Personal Health Care Index (PHC) and the Personal Consumption Expenditure Health Indexes (PCE) are recommended over the medical component of the consumer price index (CPI-M) and the GDP price index for medical care by the Medical Expenditure Panel Survey (MEPS).¹⁶⁰ While the PHC and the PCE indexes are more appropriate for estimating personal health care expenses than both the GDP price index and the CPI-M, CPI-M is the most appropriate for pooling OOP. Conversely, the GDP price index is the least appropriate in medical expenditure research.¹⁶⁰ This is due to the fact that the GDP price index includes expenditures from medical and public health research which are not useful in health care services utilization and cost estimation.¹⁶⁰ The PHC index was constructed based on the components of the CPI-M and Producer Price Index (PPI) by the CMS office of the Actuary, and the PCE was constructed from the CPI and PPI by the Bureau of Economic Analysis (BEA).¹⁶⁰

In this study, PHC was used to adjust for inflation to 2017 dollar for inpatient and outpatient costs while CPI-M was used for OOP costs. (Table 4.2) The following equation represents the formula used to obtain the 2017 U.S. dollar values.

$$2017 \text{ Dollar Value} = 2013 \text{ Dollar Value} \times 1.052 \text{ (Corresponding inflation factors)}$$

Table 4.2 CPI-M and inflation factor of medical care services from 2013 to 2017

	Inpatient		Outpatient		OOP	
Year	PHC- Hospital Care	Inflation Factor (2017/x years)	PHC- Physician/Clinical services	Inflation Factor (2017/x years)	CPI- M	Inflation Factor (2017/x years)
2013	102.2	1.052	100.1	1.000	425.1	1.118
2014	103.5	1.039	100.6	0.995	435.3	1.092
2015	104.5	1.029	99.5	1.006	446.8	1.064
2016	105.7	1.017	99.7	1.004	463.7	1.025
2017	107.5	1.000	100.1	1.000	475.3	1.00

Source: Using Appropriate Price Indices for Analyses of Health Care Expenditures or Income Across Multiple Years. Medical Expenditure Panel Survey: Agency for Healthcare Research and Quality.
https://meps.ahrq.gov/about_meps/Price_Index.shtml

4.5.2 Potential confounders

Based on the conceptual framework as adapted from the Andersen's behavioral model of health services utilization, potential confounding factors included were predisposing characteristics, enabling factors and healthcare needs. Specifically, covariates included in the multivariate regressions were predisposing characteristics (age, gender and race), enabling factors (regions, dual eligibility status) healthcare needs (Charlson Comorbidity Index (CCI), and Chronic Hepatitis C and B virus infections (HCV & HBV). Covariates were measured from Medicare beneficiary summary files and claims. This study used CCI as a measure of comorbidities which is widely used to measure the number of chronic disease comorbidities. It is calculated based on ICD-9-CM or ICD-10-CM codes identified in the Medicare database. Diabetes and HIV/AIDS were excluded from the CCI calculation. HBV/HCV was determined using HBV infection specific ICD-9-CM codes 0702, 07020, 07021, 07022, 07023, 07030, 07031, 07032, 07033, VO261¹⁶¹ or ICD-10-CM codes: B181, B1910, B189¹⁶² and HCV infection specific ICD-9-CM codes: 07054, 07044, 07070, 0707, 07071, 07041, VO262, 07051¹⁶¹ or ICD-10-CM codes: B182, B1920 and B189.¹⁶³

4.6 Propensity Score Matching

Differences in subject's baseline demographic and clinical characteristics may have influenced assignment into therapy groups, and this consequently may impact the result of this study. To minimize these differences in characteristics and selection biases, PS matching was performed for each of the therapy group pairs (1) PI use versus non-PI use and (2) PI use versus no-ART.¹⁶⁴ The PS matching approach generates a pseudo-randomized population where beneficiaries are similar in terms of their baseline characteristics and differ only by their therapy group.

Patient-specific propensity scores were estimated by fitting a logistics regression model predicting the odds of being prescribed PIs instead of (1) non-PIs and (2) no-ARTs, including covariates such as age, gender, sex, race, HCV/HBV, regions and dual eligibility. PS-matched study sample was created by matching on the propensity scores based on a 1:1 greedy matching algorithm. CCI characteristics were excluded in the PS matching to enable matching of at least 40% of the complete sample. Using 0.3 cut-off, units were matched only if the difference in the logits of the propensity scores for pairs of units from the two groups is less than or equal to 0.3 times the pooled estimate of the standard deviation. Residual unmatched beneficiaries were excluded. Balance and comparability of baseline characteristics across therapy groups were evaluated using chi-square test. P-value greater than 0.05 was considered a good balance in baseline characteristics. This study leveraged a case-control study with a PS matching methodology employed by Nussbaum *et al.*¹⁶⁵ In their study, they used PS matching approach to generate matched therapy groups- preoperative radiotherapy versus no radiotherapy and (2) postoperative therapy versus no radiotherapy and compared overall patient's survival between the matched groups.¹⁶⁵

4.7 Statistical Analysis

In study aims 1 and 2, we describe baseline characteristics of unmatched and PS matched eligible beneficiaries using chi-square test to compare covariate's balance between both therapy group pairs. Unadjusted logistic regression was performed to determine crude associations between PI use and the odds of developing T2DM for each therapy group pair, and unadjusted association within race sub-groups. In study aim 3, baseline covariates were compared between history of T2DM status using chi-square for categorical covariates. Independent two-group tests were performed to compare different costs between beneficiaries with a history of T2DM while unadjusted GLM analysis was performed to determine unadjusted impact of patients with a previous history of T2DM on different healthcare costs.

Multivariate logistic regressions were performed to determine the odds of developing T2DM and racial variations in the odds of developing T2DM. A multivariate Generalized Linear Model (GLM) was performed to determine the impact of comorbid T2DM on different health care costs. All data analysis was carried out using SAS version 9.4 (SAS Institute, Cary, NC).

4.7.1 Bivariate analysis

Therapy group pairs (PI versus non-PIs and PI versus no-ART) in both matched and complete datasets were compared using chi-square to determine balance across covariates (age, gender and race, regions, dual eligibility status, HBV & HCV and CCI). For continuous variables such as cost domains, an independent two-group t-test was used to determine mean cost differences between beneficiaries with T2DM compare to those without T2DM. Unadjusted regression was performed to determine the association between treatment with PI and the odds of developing T2DM, racial variation in odds of developing T2DM and the effect of comorbid T2DM on different healthcare costs.

Unadjusted logistics regression was performed for each therapy group pair as in Formula 4.1 to determine unadjusted odds of developing T2DM.

$$\ln(\text{odds that } Y=1) = \hat{\alpha}0 + \hat{\alpha}1 (\text{Therapy group}) + \mu_i \quad (\text{Formula 4.1})$$

★ *Y* is a dummy variable indicator for T2DM diagnosis

- 0: Negative T2DM diagnosis
- 1: Positive T2DM diagnosis

★ *Therapy groups*

- PI versus non-PI pair
 - 0: Non-PI
 - 1: Pi

- PI versus no-ART
 - 0: No-ART
 - 1: PI

In Formula 4.1, ' \hat{a}_1 ' was the coefficient for the predictor of interest. The odds ratio comparing the odds of developing T2DM between therapy groups pair was measured as ' $\exp(\hat{a}_1)$ '.

Unadjusted logistics regression was performed for each therapy group pairs to determine odds of developing T2DM using Caucasian and African American sub-groups as in Formula 4.2

$$\ln(\text{odds that } Y=1) = \hat{a}_0 + \hat{a}_1 (\text{Therapy group } [race\text{-}subgroup]) + \mu_i \quad (\text{Formula 4.2})$$

★ *Y* is a dummy variable indicator for T2DM diagnosis

- 0: Negative T2DM diagnosis
- 1: Positive T2DM diagnosis

★ *Therapy groups*

- PI versus non-PI pair
 - 0: Non-PI
 - 1: PI
- PI versus no-ART
 - 0: No-ART
 - 1: PI

In both race sub-group bivariate logistic regression model, ' \hat{a}_1 ' represents the coefficient of predictor of interest. The odds ratio comparing the odds of developing T2DM with respect to the compared therapy group pairs within Caucasian or African American subgroups was measured as ' $\exp(\hat{a}_1)$ '.

Unadjusted GLM regression was performed in Formula 4.3 to determine unadjusted impact of history of T2DM on different health care costs: (1) total Medicare costs, (2) total

prescription costs, (3) total OOP , (4) total healthcare costs, (5) total hospitalization cost and (6) total outpatient cost.

$$\text{Log } (E(Y)) = \hat{\alpha}0 + \hat{\alpha}1 (\text{Comorbid T2DM}) + \mu_i \quad (\text{Formula 4.3})$$

- ★ *Y* is a continuous variable representing each of the cost domains: Total cost of hospitalization, total outpatient costs, total Medicare costs, total prescription drug costs, total OOP and total healthcare costs.
- ★ Comorbid *T2DM* is dummy variable indicating comorbid T2DM
 - 0: No diabetes diagnosis
 - 1: Diabetes diagnosis

In each bivariate GLM regression, ‘ $\hat{\alpha}1$ ’ represents the coefficient of predictor of interest which is the estimate of percentage changes in cost between group with comorbid T2DM and group without comorbid T2DM measured as $[\exp(\hat{\alpha}1-1) * 100]$.

4.7.2 Multivariate analysis

4.6.3.1 Aim 1: Treatment with PIs and odds of developing T2DM

After generating two PS matched data sets for - (1) PI versus non-PI and (2) PI versus no-ART, multivariate logistic regression was performed as in Formula 4.4 to determine the odds of developing T2DM for each comparison pairs.

$$\text{In (odds that } Y=1) = \hat{\alpha}0 + \hat{\alpha}1 (\text{Therapy group}) + \hat{\alpha}2 (\text{Predisposing characteristics}) + \hat{\alpha}3 (\text{Enabling factors}) + \hat{\alpha}4 (\text{Healthcare need}) + \mu_i \quad (\text{Formula 4.4})$$

- ★ *Y* is a dummy variable indicator for T2DM diagnosis
 - 0: Negative T2DM diagnosis
 - 1: Positive T2DM diagnosis
- ★ *Therapy groups*

- PI versus non-PI pair
 - 0: Non-PI
 - 1: PI
- PI versus no-ART
 - 0: No-ART
 - 1: PI

★ *Predisposing characteristics* includes various demographic variables

- Age group: 1: 18-34 (Reference), 2: 35-44, 3: 45-54, 4: 55-64 and 5: > 64
- Gender: 1: Male, and 2: Female (Reference)
- Race: 1: Caucasian (Reference), 2: African Americans and 3: Others

★ *Enabling factors* includes region and residence where Medicare beneficiaries live

- Dual Eligibility Status: 0: No and 1: Yes
- Regions: 1: West, 2: South, 3: Midwest and 4: Northeast

★ *Healthcare needs*: This includes clinical characteristics variables

- Charlson Comorbidity Index (CCI): ≤ 1 , 2 and 3+
- Hepatitis C & B virus infection (HCV & HBV): positive HCV or HBV diagnosis=1 and negative HCV and HBV diagnosis=0.

In Formula 4.4, ' \hat{a}_1 ' was the coefficient for the predictor of interest. The odds ratio comparing the odds of developing T2DM between therapy groups pairs was measured as ' $\exp(\hat{a}_1)$ '.

4.6.2.2 Aim 2: Racial disparity in odds of developing T2DM following treatment with PIs

Using the PS matched data sets for - (1) PI versus non-PI comparison and (2) PI versus no-ART therapy, an analysis of Caucasian and African American race sub-groups was performed using multivariate logistic regression model to assess variations in the odds of developing T2DM for both therapy pairs within Caucasian and African American subgroups.

In Formula 4.5, a multivariate race sub-group analysis did not include race variables since

race sub-groups were being assessed. A multivariate logistic model for each therapy group pair (in Formula 4.5) was performed separately for Caucasian and African American sub-groups.

$$\ln(\text{odds that } Y=1) = \hat{\alpha}0 + \hat{\alpha}1 (\text{Therapy group [race sub-group]}) + \hat{\alpha}2 (\text{Predisposing characteristics}) + \hat{\alpha}3 (\text{Enabling factors}) + \hat{\alpha}4 (\text{Healthcare need}) + \mu_i \quad (\text{Formula 4.5})$$

★ *Y* is a dummy variable indicator for diabetes diagnosis

- 0: Negative T2DM diagnosis
- 1: Positive T2DM diagnosis

★ *Therapy groups*

- PI versus non-PIs therapy group pair
 - 0: Non-PI
 - 1: PI
- PI versus no-ART therapy group pair
 - 0: No-ART
 - 1: PI

★ *Predisposing characteristics* includes various demographic variables

- Age group: 1: 18-34 (Reference), 2: 35-44, 3: 45-54, 4: 55-64 and 5: > 64
- Gender: 1: Male, and 2: Female (Reference)

★ *Enabling factors* includes region and residence where Medicare beneficiaries live

- Regions: 1: West, 2: South, 3: Midwest and 4: Northeast
- Dual Eligibility Status: 0: No and 1: Yes

★ *Healthcare needs*: This includes clinical characteristics variables

- Charlson Comorbidity Index (CCI): ≤ 1, 2 and 3+
- Hepatitis C & B virus infection (HCV & HBV): positive HCV or HBV diagnosis=1 and negative HCV and HBV diagnosis=0.

In each of the race sub-group multivariate regression, ' $\hat{\alpha}_1$ ' represents the coefficient of the predictor of interest. The odds ratio comparing the odds of developing T2DM between the compared therapy group pairs within Caucasian or African American subgroups was measured as ' $\exp(\hat{\alpha}_1)$ '.

4.6.2.3 Aim 3: Effects of comorbid T2DM on healthcare costs

In aim 3, GLM with log link and gamma distribution was used to assess the economic burden of comorbid T2DM. Cost and utilization data are often skewed, gamma distributed, and violates independent observation assumption. These characteristics violate Ordinary Least Squares regression (OLS)-normality and homoscedasticity assumptions given that it is often right-hand skewed with significant heteroskedasticity.^{166,167} The independent observation assumption is commonly violated by cost data, given that multiple individuals using the same healthcare services may incur similar total health care costs.

Gamma GLM is suitable for modeling positively skewed data, non-negative data with variances not proportional to the square of the means and of which there are certain forms of heteroscedasticity.¹⁶⁸ In addition, it has been demonstrated in Amal Saki *et al.* that gamma GLM is a good model for estimating the population mean of healthcare cost data.¹⁶⁹ Although, non-normally distributed data could be normalized using transformations, the back transformation to the original scale may generate a biased estimate if the error term has inconsistent variance which is often the case with count data.¹⁷⁰ Even if back transformation is considered a valid approach, interpretation of results is often a concern because estimates of a transformed scale cannot generate inference to healthcare mean cost.¹⁷¹ Given the above concerns, GLM modeling is the most appropriate model to use in cost estimation because it directly models costs in its original scale, corrects possible skewed distribution of cost data, and generates estimates that can be inferred to healthcare costs.

To use a gamma GLM for this study, the decision on what link and distribution would be used in analysis of cost data is made based on statistical tests. Box-Cox procedure was performed to generate possible links that could be used for the GLM modeling as shown in Table 4.3 below.¹⁷² To determine the distribution, the modified Park test procedure on raw-scaled residuals was used to select the distribution family to be used based on the relationship between variance and mean as shown in Table 4.4 below.¹⁷² At $\lambda = 0$, the mean and variance relationship are orthogonal, thus Gaussian distributional assumption is considered. At $\lambda = 1$, mean and variance relationship are proportional, thus Poisson-like distribution assumption is considered. At $\lambda = 2$, mean and variance relationship is quadratic and thus Gamma distributional assumption is considered. At $\lambda = 3$, the mean and variance relationship are cubic thus, inverse Gaussian distributional assumption is considered.¹⁷² Based on the modified Park test performed, gamma distribution was considered for the cost analysis using GLM in this study.

Table 4.3: Link options for GLM modeling

Lambda	Links
-1	Inverse
0	Logarithm
0.5	Square Root
1	Linear
2	Square

Table 4.4: Distribution options for GLM modeling

Lambda	Mean & variance relationship	Distribution
0	Orthogonal	Gaussian NLLS
1	Proportional	Poisson
2	Quadratic	Gamma
3	Cubic	Inverse Gaussian

The GLM in Formula 4.6 was used to determine the economic burden of comorbid T2DM among HIV/AIDS positive Medicare beneficiaries. This was repeated for each of the six cost domains: (1) total Medicare costs, (2) total prescription costs, (3) total OOP, (4) total medical costs, (5) total hospitalization cost and (6) total outpatient cost.

$$\text{Log}(E(Y)) = \hat{\alpha}_0 + \hat{\alpha}_1 (\text{comorbid T2DM}) + \hat{\alpha}_2 (\text{Predisposing characteristics}) + \hat{\alpha}_3 (\text{Enabling factors}) + \hat{\alpha}_4 (\text{Healthcare need}) + \hat{\alpha}_5 (\text{Therapy group}) + \mu_i$$

(Formula 4.6)

★ *Y* is a continuous variable representing each of the cost domains: Total cost of hospitalization, total outpatient costs, total Medicare costs, total prescription drug costs, total OOP and total healthcare costs.

★ *Comorbid T2DM* is dummy variable indicating comorbid T2DM

- 0: No diabetes diagnosis
- 1: Diabetes diagnosis

★ *Therapy groups*

- PI versus non-PIs therapy group pair
 - 0: Non-PI
 - 1: PI

✧ *Predisposing characteristics* includes various demographic variables

- Age group: 1: 18-35 (Reference), 2: 35-44, 3: 45-54, 4: 55-64 and 5: > 64
- Gender: 1: Male, and 2: Female (Reference)
- Race: 1: Caucasian (Reference), 2: African Americans and 3: Others

✧ *Enabling factors* includes region and residence where Medicare beneficiaries live

- Regions: 1: West, 2: South, 3: Midwest and 4: Northeast
- Dual Eligibility Status: 0: No and 1: Yes

✧ *Healthcare needs*: This includes clinical characteristics variables

- Charlson Comorbidity Index (CCI): ≤ 1 , 2 and 3+
- Hepatitis C & B virus infection (HCV & HBV): positive HCV or HBV diagnosis=1 and negative HCV and HBV diagnosis=0.

In each multivariate GML regression, ' $\hat{\alpha}_1$ ' represents the coefficient of a predictor of interest, which is the estimate of percentage changes in cost between groups with a comorbid T2DM and groups without a comorbid T2DM measured as ' $\exp(\hat{\alpha}_1 - 1) * 100$ '.

4.8 Sensitivity Analysis

We performed sensitivity analysis to evaluate the robustness of the results in aim 1 and 2 to possible analytical perturbations resulting from the matching approach used. Specifically, PS matching approach includes only the matched subjects in the final matched dataset and exclude unmatched subjects, which could impact the main results. To evaluate the sensitivity of these exclusions on the main results, logistic regressions were re-fitted using the inverse probability-of-treatment weighting (IPTW) (instead of matching) which is a type of PS analytical methods that uses the full sample in the analysis.

IPTW uses PSs to form weights and create a pseudo-population in which the baseline characteristics and assignment to PI treatment are independent of each other (mimicking the

randomization setting). The term pseudo-population assumes that the weighted group could have been generated from a population in which there was no confounding.¹⁷³ IPTW is performed by estimating each individual's probability (PS) to be assigned to their respective treatment groups (either PI or non-PI) based on observed characteristics, and then generate weight by the inverse of this estimated PS. Beneficiaries treated with PIs are assigned a weight of $1/p(Z=1|X)$, and beneficiaries treated with the control (non-Pi or no-ART) are assigned a weight of $1/(1-p(Z=1|X))$, where Z is a binary treatment indicator (PI-status) and X is a vector of observed baseline characteristics.¹⁷³ The generated weight were stabilized to avoid extreme weights which may results in an analysis that is dependent on a few individuals with extreme weights.¹⁷³

CHAPTER 5

RESULTS

The results of this dissertation are shown in three major sections in this chapter. The first section includes the sample selection flow chart (used for study aim 1 and 2), the descriptive and multivariate results for study aim 1. Section two contains the descriptive and multivariate results of aim 2. Section three includes the sample selection flow chart, descriptive and multivariate results.

5. 1 Treatment with PI and Development of T2DM

Figure 5.1 describes the flow chart of the sample selections, baseline demographic and clinical characteristics of Medicare beneficiaries with HIV/AIDS. It also presents the multivariate results of PI use on the odds of developing T2DM.

5.1.1 Flow chart for sample selection for aim 1 and 2

Using 2013 to 2017 Medicare data with 1 million Medicare beneficiaries, we generated study aims 1 and 2 samples in three main segments as shown in figure 5.1. First, we identified 2,627 beneficiaries with diagnosis of HIV/AIDS from the Medicare outpatient and inpatient files. Second, we identified 182,007 beneficiaries with diagnosis of T2DM from the Medicare outpatient and inpatient file. Exactly 66,388 beneficiaries with diagnosis during the washout period (Jan 1 to July 1, 2013) were excluded, resulting in a total of 115,619 beneficiaries with T2DM. We excluded a total of 115,100 beneficiaries who had no record of HIV/AIDS diagnosis, to obtain a sample of 2,627 HIV/AIDS beneficiaries, which were either diagnosed with T2DM (case) or not (control). Third, a total of 183 beneficiaries were excluded if (1), they were enrolled in an HMO

plan or (2), if they were not continuously enrolled in Part A and B plan resulting in 2,444 beneficiaries with HIV/AIDS. After excluding 91 beneficiaries diagnosed of T2DM before treatment with PIs, a total of 2,353 HIV/AIDS positive beneficiaries were selected in the final sample. The final sample consists of 342 HIV/AIDS positive beneficiaries with diagnosis of T2DM (case) and 2,011 HIV/AIDS positive beneficiaries without a diagnosis of T2DM (control).

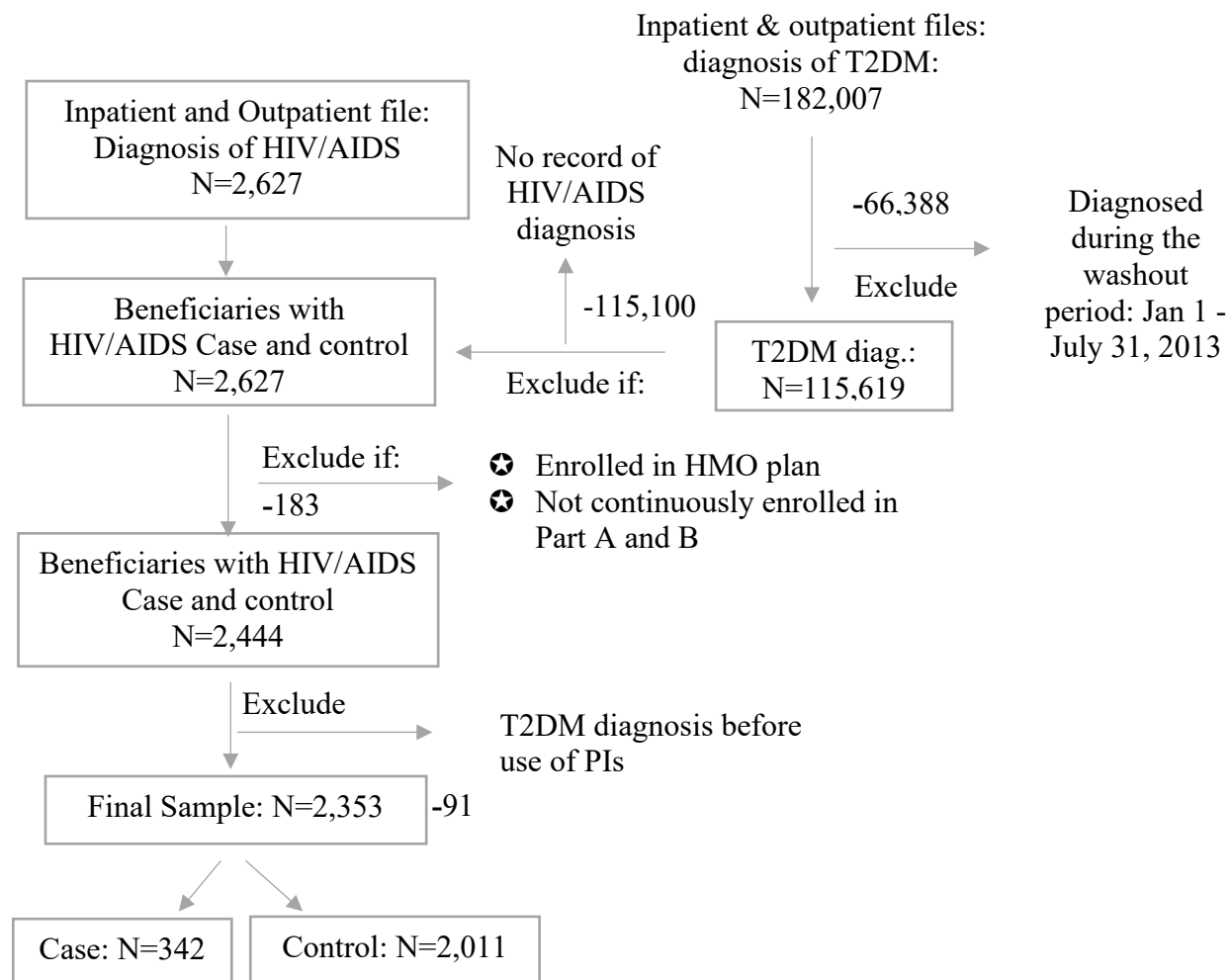


Figure 5.1 Sample selection flow chart for study aims 1 & 2

5.1.2 Baseline characteristics of matched and unmatched samples

5.1.2.1 PI versus non-PIs

Table 5.1 below shows a comparison of baseline demographic and clinical characteristics of beneficiaries between PI and non-PI therapy groups for both matched and unmatched selected beneficiaries. In the complete sample, beneficiaries treated with PIs significantly differ from beneficiaries treated with non-PIs in terms of age groups (65+ years: 21.2 % vs. 28.5 %; $p=0.001$), race category (Caucasians: 42.1 % vs. 49.5 %; $p=0.007$), CCI (3+: 34.1 % vs. 28.9 %; $p=0.036$) and dual eligibility status ($p=0.0548$). However, both groups are similar in terms of gender (female: 24.8 % vs. 27.0 %; $p=0.284$), census region (Midwest: 15.9 % vs. 18.7 %; $p=0.100$) and HBV/HCV status (Positive: 27 % vs. 25.9%; $p=0.598$).

A total of 484 beneficiaries per group were matched after 1:1 greedy PS matching, based on age, gender, race, region, HBV/HCV, and dual eligibility characteristics. Beneficiary characteristics included in the PS matching were balanced between both PI and non-PI therapy groups- age group (65+ years: 28.3 % vs. 28.3%, $p=1.000$), gender (female: 22.9 % vs. 22.9 %, $p=1.000$), race category (Caucasians: 49.0 % vs. 49.0 %; $p=1.000$), census region (Midwest: 16.1% vs. 16.1 %; $p=1.000$), HBV/HCV (positive: 7.4 % vs. 7.4 %; $p=1.000$) and dual eligibility (yes: 62.6 % vs. 62.6 %; $p=1.000$). CCI factors were not included in the matching. Beneficiaries treated with PIs significantly vary from those treated with non-PIs in terms CCI (3+: 32.2% vs. 22.3 %; $p= <.0001$

Table 5.1. Baseline characteristics of beneficiaries treated with PIs vs. non-PIs: Complete and matched sample

PI versus non-PI comparison										
Complete Dataset						Matched Dataset				
	PIs	(n=1005)	Non-PI (n=766)		P-Values	PIs (n=484)		Non-PIs (n=484)		P-Values
	N	%	N	%		N	%	N	%	
Age Group										
18 - 44 (Ref.)	152	15.1	103	13.5	0.001	87	18.4	87	18.4	1.000
45 - 54	331	32.9	204	26.6		109	22.5	109	22.5	
55 - 64	309	30.8	241	31.5		150	30.9	150	30.9	
65+	213	21.2	218	28.5		138	28.3	138	28.3	
Gender										
Male	756	75.2	559	73.0	0.284	373	77.1	373	77.1	1.000
Female	249	24.8	207	27.0		111	22.9	111	22.9	
Race										
Caucasian	423	42.1	379	49.5	0.007	237	49.0	237	49.0	1.000
African America	494	49.2	334	43.6		218	45.0	218	45.0	
Other Race	88	8.8	53	6.9		29	6.0	29	6.0	
Census Region										
Midwest	160	15.9	143	18.7	0.100	78	16.1	78	16.1	1.000
Northeast	217	21.6	189	24.7		93	19.2	93	19.2	
South	467	46.5	326	42.6		225	46.5	225	46.5	
West	161	16.0	108	14.1		88	18.2	88	18.2	
Hepatitis B & C Virus										
Negative	734	73.0	568	74.2	0.598	448	92.6	448	92.6	1.000
Positive	271	27.0	198	25.9		36	7.4	36	7.4	

Charleson Comorbidity Index										
≤1 (Ref.)	358	35.6	311	40.6		186	38.4	251	51.9	
2	304	30.3	234	30.6	0.036	142	29.3	125	25.8	<.0001
3+	343	34.1	221	28.9		156	32.2	108	22.3	
Dual Eligibility Status										
No	197	19.6	179	23.4	0.0548	181	37.4	181	37.4	1.000
Yes	808	80.4	587	76.6		303	62.6	303	62.6	
PI: Protease Inhibitors, ART: Anti-Retroviral Therapy										

5.1.2.2 PI versus no-ART

Table 5.2 compares beneficiary's baseline demographics and clinical characteristics between the group treated with PIs and those not treated with ART for both matched and unmatched selected beneficiaries. For the unmatched sample, some of the clinical and demographic characteristics of beneficiaries in the PI therapy group are different from beneficiaries in the no-ART therapy group -age groups (65+ years: 21.2 % vs. 38.1 %; $p<0.0001$), gender (female: 24.8 % vs. 29.7 %; $p=0.032$), race category (Caucasians: 42.1 % vs. 54.5 %; $p<.0001$), CCI (3+: 34.1 % vs. 23.2 %; $p<.0001$) and dual eligibility status (Yes: 80.4 % vs. 52.2 %; $p<.0001$). However, both groups are similar in terms of beneficiaries' census region (Midwest: 15.9 % vs. 15.8 %; $p=0.629$) and HBV & HCV status (Positive: 22.7 % vs. 22.7%; $p=0.998$). A total of 496 beneficiaries per group were matched after 1:1 greedy PS matching, based on age, gender, race, region, HBV/HCV, and dual eligibility characteristics. For the PS matched sample, beneficiary characteristics included in the PS matching were balanced between both PI and no-ART therapy group pairs - age group (65+ years: 27.8 % vs. 27.8 %, $p=1.000$), gender (female: 24.1 % vs. 24.1 %, $p=1.000$), race category (Caucasians: 42.7 % vs. 42.7 %; $p=1.000$), census region (Midwest: 16.9% vs. 16.9 %; $p=1.000$), HBV & HCV (positive: 6.7 % vs. 6.7 %; $p=1.000$) and dual eligibility (yes: 64.9 % vs. 64.9 %; $p=1.000$). Beneficiaries in the PI therapy group significantly vary from those in no-ART therapy group in terms CCI (3+: 33.7 % vs. 22.9 %; $p<.0001$) which was not included in the PS match

Table 5.2 Baseline characteristics of beneficiaries treated with PIs vs. No-ART therapy groups: Complete and matched sample

PI versus No-ART Naive comparison										
	Complete Dataset					Matched Dataset				
	PIs (n=1005)		No-ART (n=582)		P-Values	PIs (n=490)		No-ART (n=490)		P-Values
	N	%	N	%		N	%	N	%	
Age Group										
18 - 44 (Ref.)	152	15.1	89	15.3	<.0001	87	17.8	87	17.8	1.000
45 - 54	331	32.9	109	18.7		114	23.3	114	23.3	
55 - 64	309	30.8	162	27.8		153	31.2	153	31.2	
65+	213	21.2	222	38.1		136	27.8	136	27.8	
Gender										
Male	756	75.2	409	70.3	0.032	372	75.9	372	75.9	1.000
Female	249	24.8	173	29.7		118	24.1	118	24.1	
Race										
Caucasian	423	42.1	317	54.5	<.0001	209	42.7	209	42.7	1.000
African America	494	49.2	226	38.8		245	50.0	245	50.0	
Other Race	88	8.8	39	6.7		36	7.4	36	7.4	
Census Region										
Midwest	160	15.9	91	15.9	0.629	83	16.9	83	16.9	1.000
Northeast	217	21.6	126	22.0		96	19.6	96	19.6	
South	467	46.7	251	43.8		217	44.3	217	44.3	
West	161	16.0	105	18.3		94	19.2	94	19.2	
Hepatitis B & C Virus										
Negative	777	77.3	450	77.3	0.998	457	93.3	457	93.3	1.000

Positive	228	22.7	132	22.7		33	6.7	33	6.7	
Charleson Comorbidity Index										
≤1 (Ref.)	358	35.6	295.0	50.7		177	36.1	248	50.6	
2	304	30.3	152.0	26.1	<.0001	148	30.2	130	26.5	<.0001
3+	343	34.1	135.0	23.2		165	33.7	112	22.9	
Dual Eligibility Status										
No	197	19.6	278	47.8	<.0001	172	35.1	172	35.1	1.000
Yes	808	80.4	304	52.2		318	64.9	318	64.9	
PI: Protease Inhibitors, ART: Anti-Retroviral Therapy										

5.1.3 Distribution of PI class prescription

Figure 5.1 below shows the distribution of PI prescription by sub-class for the full sample. Among selected beneficiaries who were treated with PIs, ritonavir was the most frequently prescribed PI (n=388) followed by darunavir (n=236), atazanavir (n=170) and lopinavir/ritonavir combination (n=151). Fosamprenavir calcium and nelfinavir mesylate have similar PI prescription distributions- (n=30) and (n=21) respectively. Indinavir sulfate, tipranavir and saquinavir mesylate were the least prescribed PI sub-class with frequencies-n=2, 3 and 4 respectively.

Figure 5.2 below shows the distribution of PI prescriptions by sub-class in the matched sample. After matching, the distribution of PI prescriptions was consistent with the distribution in the full sample. Ritonavir was the most frequently prescribed PI (n=184) followed by darunavir (n=112), atazanavir (n=81) and lopinavir/ritonavir combination (n=73). While fosamprenavir calcium and nelfinavir have similar prescription distribution -n=18 and 12 respectively, tipranavir, indinavir sulfate and saquinavir mesylate were the least prescribed PI sub-class with frequencies-n=1, 2 and 3, respectively.

Figure 5.2 below shows the distribution of PI prescription by sub-class for the full sample. Among selected beneficiaries who were treated with PIs, ritonavir was the most frequently prescribed PI (n=388) followed by darunavir (n=236), atazanavir (n=170) and lopinavir/ritonavir combination (n=151). Fosamprenavir calcium and nelfinavir mesylate have similar PI prescription distributions- (n=30) and (n=21) respectively. Indinavir sulfate, tipranavir and saquinavir mesylate were the least prescribed PI sub-class with frequencies-n=2, 3 and 4 respectively. Figure 5.3 below shows the distribution of PI prescriptions by sub-class in the matched sample. After matching, the distribution of PI prescriptions was consistent with the distribution in the full sample.

Ritonavir was the most frequently prescribed PI (n=184) followed by darunavir (n=112), atazanavir (n=81) and lopinavir/ritonavir combination (n=73). While fosamprenavir calcium and nelfinavir have similar prescription distribution -n=18 and 12 respectively, tipranavir, indinavir sulfate and saquinavir mesylate were the least prescribed PI sub-class with frequencies-n=1, 2 and 3 respectively.

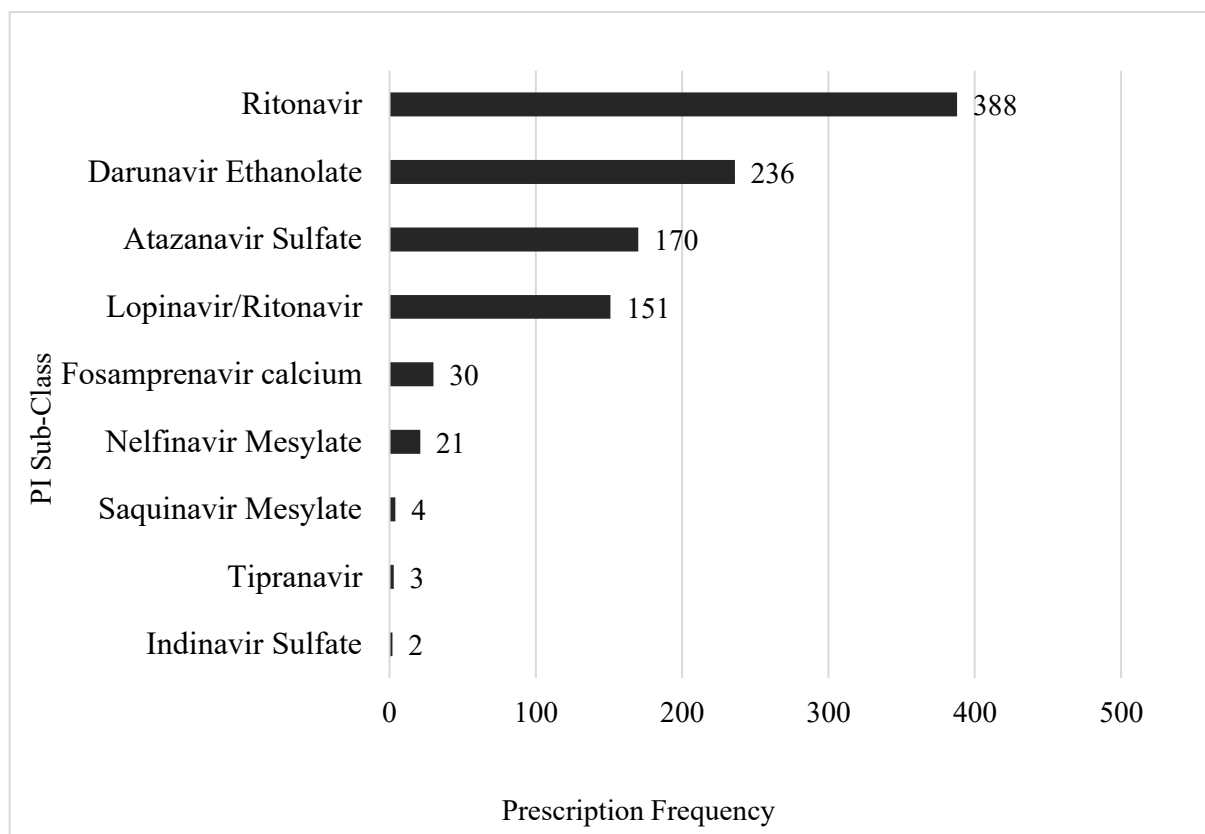


Figure: 5.2 Distribution of PI prescription class: Unmatched sample (PI: n=1005)

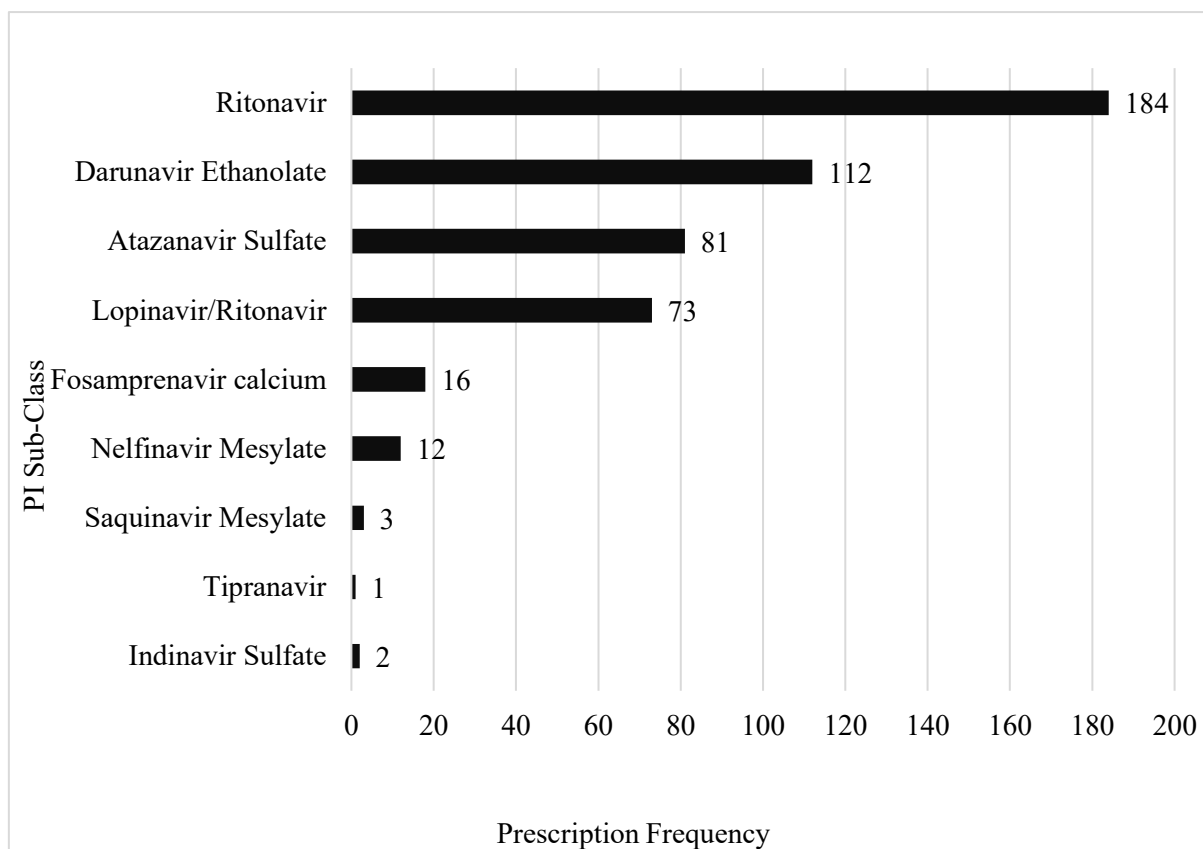


Figure: 5.3 Distribution of PI class prescription: Matched sample (PI: n=484)

5.1.4 Unadjusted logistic regression analysis

Table 5.3 presents the results of unadjusted logistic regression comparing the odds of developing T2DM between PI versus non-PI therapy groups and PIs versus no-ART therapy group. Bivariate analysis shows that the odds of developing T2DM was 2.06 times higher in beneficiaries treated with PIs than beneficiaries treated with non-PIs (OR:2.06; 95% CI: 1.39-3.06). In the PI versus no-ART therapy pair, unadjusted results show that the odds of developing T2DM was 2.13 times higher in beneficiaries treated with PIs compared to those not treated with ART (OR:2.13; 95% CI: 1.45-3.14).

Table 5.3 Unadjusted association between PI and development of T2DM

	OR	95 % CI		P-Value
Medication Exposure				
Non-PIs (Ref)				
PIs	2.06	1.39	3.06	0.0003
Medication Exposure				
ART Naïve (Ref)				
PIs	2.13	1.45	3.14	0.0001

PI: Protease Inhibitors, OR: Odds ratio, T2DM: Types II diabetes Mellitus, ART: Anti-Retroviral Therapy, CI: Confidence Interval

5.1.5 Adjusted logistic regression analysis

5.1.5.1 PIs versus non-PIs

In the adjusted logistic regression analysis, we controlled for potential confounding factors at the baseline. (Table 5.4) We found that the odds of developing T2DM between beneficiaries treated with PIs and those treated with non-PIs was still significant after adjusting for potential confounders.

Compared to beneficiaries treated with non-PIs, those treated with PIs were 76 % more likely to develop T2DM after adjusting for covariates (OR=1.76; 95% CI: 1.17-2.64). Only, CCI of 3+ were statistically significantly associated with the development of T2DM. Compared to beneficiaries with comorbidity of ≤ 1 , those with a comorbidity of 3 or more were 2.93 times more likely to develop T2DM after adjusting for covariates.

Table 5.4 Adjusted logistic regression analysis of factors associated with development of T2DM: PIs versus non-PIs therapy group

	AOR	95 % CI		P-Value
Medication Exposure				
Non-PIs (Ref)				
PIs	1.76	1.17	2.64	0.0066
Age Group				
18 - 44 (Ref.)				
45 - 54	1.20	0.64	2.27	0.6889
55 - 64	1.00	0.54	1.85	0.4946
65+	1.31	0.70	2.46	0.3646
Gender				
Female (Ref)				
Male	0.98	0.63	1.54	0.9313
Race				
Caucasian (Ref)				
African America	1.35	0.87	2.09	0.9811
Other Race	1.84	0.88	3.82	0.1966
Census Region				
Midwest (Ref)				
Northeast	1.04	0.54	2.00	0.6676
South	0.88	0.46	1.67	0.6700
West	0.90	0.51	1.60	0.7382
Hepatitis B & C Virus				
Negative (Ref)				
Positive	1.57	0.82	3.00	0.1741
Charleson Comorbidity Index				
≤1 (Ref)				
2	1.81	1.08	3.05	0.7948
3+	2.93	1.79	4.82	0.0002
Dual Eligibility Status				
No (Ref)				
Yes	1.64	1.03	2.61	0.0370

PIs:Protease Inhibitors, AOR: Adjusted Odds ratio, T2DM: Types II diabetes Mellitus, CI: Confidence Interval

5.1.5.2 PIs versus no-ARTs

In the adjusted logistic regression analysis, we controlled for potential confounding factors at the baseline. (Table 5.5) We found that treatment with PIs was still significantly associated with higher odds of developing T2DM compared to beneficiaries not treated with ARTs, after adjusting for covariate. Compared to beneficiaries in the no-ARTs therapy group,

those treated with PIs were 87 % more likely to develop T2DM after adjusting for covariates (OR=1.87; 95% CI: 1.25-2.81). Covariates statistically significantly associated were CCI of 3+ and dual eligibility status. Compared to beneficiaries with comorbidity of ≤ 1 , those with comorbidity of 3 or more were 3.58 times more likely to develop T2DM after adjusting for covariates (OR=3.58; 95% CI: 2.22-5.76). After adjusting for covariates, beneficiaries who are eligible to Medicare and Medicaid were 1.55 times more likely to develop T2DM compare to beneficiaries who are not dual eligible.

Table 5.5 Adjusted logistic regression analysis of factors associated with development of T2DM: PIs versus no-ARTs

	AOR	95 % CI		P-Value
Medication Exposure				
No-ART (Ref)				
PIs	1.87	1.25	2.81	0.0025
Age Group				
18 - 44 (Ref.)				
45 - 54	1.00	0.54	1.85	0.6697
55 - 64	0.79	0.42	1.49	0.3241
65+	0.95	0.50	1.84	0.8894
Gender				
Female (Ref)				
Male	0.91	0.59	1.41	0.6766
Race				
Caucasian (Ref)				
African America	1.64	1.08	2.50	0.5663
Other Race	2.02	0.92	4.46	0.2363
Census Region				
Midwest (Ref)				
Northeast	1.23	0.60	2.49	0.7696
South	1.14	0.57	2.25	0.9351
West	1.27	0.70	2.31	0.5259
Hepatitis B & C Virus				
Negative (Ref)				
Positive	0.91	0.47	1.77	0.7786
Charleson Comorbidity Index				
≤1 (Ref.)				
2	1.60	0.95	2.71	0.4623
3+	3.58	2.22	5.76	<.0001
Dual Eligibility Status				
No (Ref)				
Yes	1.55	0.99	2.43	0.0565

PI: Protease Inhibitors, AOR: Adjusted Odds ratio, T2DM: Types II diabetes Mellitus, ART: Anti-Retroviral Therapy, CI: Confidence Interval

5.2 Racial Disparity In Development of T2DM Following Treatment With PI

Table 5.6 presents the description of matched samples of African American and Caucasian Medicare beneficiaries with HIV/AIDS across each comparison group, the unadjusted race-subgroup logistic regression of treatment with PIs and development of T2DM, and the multivariate race-subgroup logistic regression of treatment with PIs and development of T2DM for each comparison group.

5.2.1 Descriptive Analysis

Tables 5.6 ad 5.7 shows chi-square test results comparing baseline characteristics of matched sample of African Americans and Caucasians for balance across PIs versus non-PIs and PIs versus no-ARTs therapy groups.

5.2.1.1 PIs versus non-PIs

Matched sample of African American sub-groups consists of a total of 218 beneficiaries per group which are similar in terms of their clinical and demographic characteristics - age group (65+ years: 31.7 % vs. 31.7 %, $p=1.000$), gender (female: 33 % vs. 33 %, $p=1.000$), census region (Midwest: 14.7% vs. 14.7 %; $p=1.000$), HBV & HCV (positive: 23.4 % vs. 23.4 %; $p=1.000$) and dual eligibility (Yes: 68.8 % vs. 68.8 %; $p=1.000$). (Table 5.6) CCI characteristics were not included in the propensity matching process thus, beneficiaries in the PIs therapy group were significantly different from beneficiaries in the non-PIs therapy group in terms of CCI characteristics. CCI (3+: 41.3 % vs. 26.2 %; $p= 0.001$).

Within the Caucasian sub-group, a total of 237 Caucasian beneficiaries per therapy group were matched. (Table 5.6) Matched groups are similar in terms of their clinical and demographic characteristics - age group (65+ years: 35.5 vs. 35.5 %, $p=1.000$), gender (female: 14.4 % vs. 14.4 %, $p=1.000$), census region (Midwest: 18.6 % vs. 18.6 %; $p=1.000$),

HBV & HCV (positive: 7.2 % vs. 7.2 %; $p=1.000$) and dual eligibility (yes: 56.1 % vs. 56.1 %; $p=1.000$). Beneficiaries in the PIs therapy group were significantly different from beneficiaries in the non-PIs therapy group in terms of CCI characteristics. CCI (3+: 30.4 % vs. 19.4 %; $p= 0.005$).

Table 5.6 Baseline characteristics of matched sample of African American and Caucasian: PIs versus non-PIs

	African Americans					Caucasians				
	PIs (n=218)		Non-PIs (n=218)		P	PIs (n=237)		Non-PIs (n=237)		P
Covariates	N	%	N	%		N	%	N	%	
Age Group										
18 - 44 (Ref.)	43	19.7	43	19.7	1.000	32	13.5	32	13.5	1.00
45 - 54	38	17.4	38	17.4		53	22.4	53	22.4	
55 - 64	68	31.2	68	31.2		69	29.1	69	29.1	
65+	69	31.7	69	31.7		83	35.0	83	35.0	
Gender										
Male	146	67.0	146	67.0	1.000	203	85.7	203	85.7	1.000
Female	72	33.0	72	33.0		34	14.4	34	14.4	
Census Region										
Midwest	32	14.7	32	14.7	1.000	44	18.6	44	18.6	1.000
Northeast	43	19.7	43	19.7		41	17.3	41	17.3	
South	125	57.3	125	57.3		92	38.8	92	38.8	
West	18	8.3	18	8.3		60	25.3	60	25.3	
Hepatitis B & C Virus										
Negative	167	76.6	167	76.6	1.000	220	92.8	220	92.8	1.000
Positive	51	23.4	51	23.4		17	7.2	17	7.2	
Charlson Comorbidity Index										
≤1 (Ref.)	76	34.9	110	50.5	0.001	92	38.8	124	52.3	0.005
2	52	23.9	51	23.4		73	30.8	67	28.3	
3+	90	41.3	57	26.2		72	30.4	46	19.4	
Dual Eligibility Status										
No	68	31.2	68	31.2	1.000	104	43.9	104	43.9	1.000
Yes	150	68.8	150	68.8		133	56.1	133	56.1	

PI: Protease Inhibitors, ART: Anti-Retroviral Therapy

5.2.1.2 PIs versus no-ARTs

Matched sample of African American sub-groups consists of a total of 245 beneficiaries per group. (Table 5.7) Beneficiaries in the PIs therapy group were similar in terms of their clinical and demographic characteristics - age group (65+ years: 22.5 % vs. 22.5 %, $p=1.000$), gender (female: 30.2 % vs. 30.2 %, $p=1.000$), census region (Midwest: 16.0% vs. 16.0 %; $p=1.000$), HBV & HCV (positive: 7.8 % vs. 7.8 %; $p=1.000$) and dual eligibility (Yes: 73.1 % vs. 73.1 %; $p=1.000$) compared to beneficiaries in the no-ARTs therapy group. CCI characteristics were not included in the propensity matching process thus, beneficiaries in the PIs group were significantly different from beneficiaries in the non-PIs group in terms of CCI characteristics. CCI (3+: 37.1 % vs. 25.8 %; $p= 0.003$).

Within the Caucasian sub-group, a total of 209 Caucasian beneficiaries per therapy group were matched. (Table 5.7) Matched groups are similar in terms of their clinical and demographic characteristics - age group (65+ years: 34.5 % vs. 34.5 %, $p=1.000$), gender (female: 13.4 % vs. 13.4 %, $p=1.000$), census region (Midwest: 19.1 % vs. 19.1 %; $p=1.000$), HBV & HCV (positive: 5.7 % vs. 5.7 %; $p=1.000$) and dual eligibility (yes: 53.1 % vs. 53.1%; $p=1.000$). Beneficiaries in the PIs therapy group were significantly different from beneficiaries in the no-ARTs therapy group based on CCI characteristics. CCI (3+: 31.1 % vs. 21.4 %; $p= 0.008$).

Table 5.7 Baseline characteristics of matched sample of race subgroups: PIs versus no-ARTs

	African American					Caucasians				
	PIs (n=245)		Non-PIs (n=245)		P	PIs (n=209)		ART Naive (n=209)		P
	N	%	N	%		N	%	N	%	
Age Group										
18 - 44 (Ref.)	60	24.5	60	24.5	1.000	19	9.1	19	9.1	1.000
45 - 54	53	21.6	53	21.6		50	23.9	50	23.9	
55 - 64	77	31.4	77	31.4		68	32.5	68	32.5	
65+	55	22.5	55	22.5		72	34.5	72	34.5	
Gender										
Male	171	69.8	171	69.8	1.000	181	86.6	181	86.6	1.000
Female	74	30.2	74	30.2		28	13.4	28	13.4	
Census Region										
Midwest	38	15.5	38	15.5	1.000	40	19.1	40	19.1	1.000
Northeast	48	19.6	48	19.6		38	18.2	38	18.2	
South	142	58.0	142	58.0		68	32.5	68	32.5	
West	17	6.9	17	6.9		63	30.1	63	30.1	
Hepatitis B & C Virus										
Negative	226	92.2	226	92.2	1.000	197	94.3	197	94.3	1.000
Positive	19	7.8	19	7.8		12	5.7	12	5.7	
Charlson Comorbidity Index										
≤1 (Ref.)	86	35.1	100	50.5	0.003	77	36.8	132	50.4	0.008
2	68	27.8	47	23.7		67	32.1	74	28.2	
3+	91	37.1	51	25.8		65	31.1	56	21.4	
Dual Eligibility Status										
No	66	26.9	66	26.9	1.000	98	46.9	98	46.9	1.000
Yes	179	73.1	179	73.1		111	53.1	111	53.1	

PI: Protease Inhibitors, ART: Anti-Retroviral Therapy

5.2.2 Unadjusted logistic regression analysis

Table 5.8 shows the results of unadjusted logistic regression of the odds of developing T2DM between therapy group pairs for African American and Caucasian race subgroups. In the PIs versus non-PIs therapy groups, results show that the odds of developing T2DM is 2.00 times higher in African American beneficiaries treated with PIs compared to African Americans treated with non-PIs (OR:2.00; 95% CI:1.14 – 3.52). Caucasians treated with PIs are 98 % more likely to develop T2DM than Caucasians treated with non-PIs (OR:1.98; 95% CI:1.07-3.65).

In the PIs versus no-ARTs therapy groups, the odds of developing T2DM is 2.23 times higher among African Americans treated with PIs compared to African Americans who were not treated with ART (OR:2.23; 95% CI:1.17 -4.25). The odds of developing T2DM is 2.18 times higher in Caucasian beneficiaries treated with PIs compared to those not treated with ARTs (OR:2.18; 95% CI: 1.29-3.69).

Table 5.8 Unadjusted association between PI use and development of T2DM: Race Sub-group

	African Americans			P-Value	Caucasians			P-Value
	OR	95 % CI			OR	95 % CI		
Medication Exposure								
Non-PI (Ref)								
PIs	2.00	1.14	3.52	0.0158	1.98	1.07	3.65	0.0293
Medication Exposure								
ART Naive (Ref)								
PIs	2.23	1.17	4.25	0.0150	2.18	1.29	3.69	0.0037

PI: Protease Inhibitors, OR: Odds ratio, T2DM: Types II diabetes Mellitus, ART: Anti-Retroviral Therapy, CI: Confidence Interval

5.2.3 Multivariate sub-group analysis

Tables 5.9 and 5.10 show the multivariate logistic results of race sub-group analysis of PIs use on the development of T2DM for both therapy groups.

5.2.3.1 PIs versus non-PIs

In the adjusted logistic regression for race/ethnicity sub-group analysis, we controlled for potential confounding factors at the baseline. (Table 5.9) We found that among African Americans, the odds of developing T2DM between beneficiaries treated with PIs and those treated with non-PIs was still significant after adjusting for potential confounders. Compared to African American beneficiaries treated with non-PIs, those treated with PIs were 86 % more likely to develop T2DM after adjusting for covariates (OR=1.86; 95% CI: 1.03-3.36). Among other factors controlled, only CCI of 3+ were statistically significantly associated with the development of T2DM. Compared to African American beneficiaries with comorbidity of ≤ 1 , those with a comorbidity of 3 or more were 2.67 times more likely to develop T2DM after adjusting for covariates (OR=2.67; 95% CI: 1.31-5.42). Compared to African American beneficiaries with without dual eligibility, those with dual eligibility were 2.34 times more likely to develop T2DM after adjusting for covariates (OR=2.34; 95% CI: 1.10-4.95).

Among Caucasian beneficiaries, the odds of developing T2DM between beneficiaries treated with PIs and those treated with non-PIs was still significant after adjusting for potential confounders. Compared to Caucasian beneficiaries treated with non-PIs, those treated with PIs were 3.38 times more likely to develop T2DM after adjusting for covariates (OR=1.81; 95% CI: 1.02-3.22). Among other factors controlled, only CCI of 3+ were statistically significantly associated with the development of T2DM. Compared to African American beneficiaries with comorbidity of ≤ 1 , those with a comorbidity of 3 or more were 3.38 times more likely to develop T2DM after adjusting for covariates (OR=3.38; 95% CI: 1.67-6.84).

Table 5.9. Multivariate logistic regression analysis of factors associated with development of T2DM: Race sub-group comparison of PI versus non-PI therapy group

	African Americans				Caucasians			
	AOR	95 % CI		P	AOR	95 % CI		P
Medication Exposure								
Non-PIs (Ref)								
PIs	1.86	1.03	3.36	0.0390	1.81	1.02	3.22	0.0427
Age Group								
18 - 44 (Ref.)								
45 - 54	2.26	0.93	5.48	0.1568	0.55	0.22	1.38	0.4374
55 - 64	1.61	0.69	3.77	0.9577	0.50	0.20	1.23	0.2225
65+	1.76	0.71	4.38	0.6861	0.75	0.31	1.84	0.6330
Gender								
Female (Ref)								
Male	0.90	0.50	1.63	0.7304	1.05	0.52	2.14	0.8864
Census Region								
Midwest (Ref)								
Northeast	0.98	0.30	3.23	0.8995	1.01	0.44	2.30	0.7150
South	0.94	0.29	3.02	0.9740	0.76	0.33	1.75	0.5291
West	0.87	0.30	2.49	0.6961	0.89	0.43	1.83	0.9289
Hepatitis C Virus								
Negative (Ref)								
Positive	2.16	0.91	5.17	0.0827	1.07	0.38	3.04	0.8963
Charlson Comorbidity Index								
≤1 (Ref.)								
2	2.29	1.08	4.83	0.2734	1.40	0.67	2.93	0.3970
3+	2.67	1.31	5.42	0.0489	3.38	1.67	6.84	0.0006
Dual Eligibility Status								
No (Ref)								
Yes	2.34	1.10	4.95	0.0266	1.44	0.77	2.71	0.2586

PI: Protease Inhibitors, AOR: adjusted odds ratio, T2DM: Types II diabetes Mellitus, CI: Confidence Interval

5.2.3.2 PIs versus no-ARTs

We controlled for potential confounding factors at the baseline in the adjusted logistic regression for the race/ethnicity sub-group analysis. (Table 5.10). Results show that among African Americans, the odds of developing T2DM between beneficiaries treated with PI and those not treated with ART was still significant after adjusting for potential confounders.

Compared to African American beneficiaries not treated with ART, those treated with PIs were 2.05 times more likely to develop T2DM after adjusting for covariates (OR=2.05; 95% CI: 1.03-4.09). Among other factors controlled, only CCI of 3+ was statistically significantly associated with the development of T2DM. African American beneficiaries with a comorbidity of ≤ 1 were 4.66 times more likely to develop T2DM than those with a comorbidity of 3 or more after adjusting for covariates.

Among Caucasian beneficiaries, the odds of developing T2DM between beneficiaries treated with PI and those not treated with ART was still significant after adjusting for potential confounders. Compared to Caucasian beneficiaries not treated with ART, those treated with PIs were 1.96 times more likely to develop T2DM after adjusting for covariates (OR=1.96; 95% CI: 1.14-3.39). Among factors that were controlled in the logistic regression, only CCI of 3+ were statistically significantly associated with the development of T2DM. Caucasian beneficiaries with a comorbidity of ≤ 1 were 2.83 times more likely to develop T2DM than those with a comorbidity of 3 or more after adjusting for covariates (OR=2.38; 95% CI: 1.52-5.27).

Table 5.10 Multivariate logistic regression analysis of factors associated with development of T2DM: Race sub-group comparison of PI versus no-ARTs

	African Americans				Caucasians			
	AOR	95 % CI		P	AOR	95 % CI		P
Medication Exposure								
No-ART (Ref)								
PIs	2.05	1.03	4.09	0.0414	1.96	1.14	3.39	0.0158
Age Group								
18 - 44 (Ref.)								
45 - 54	0.46	0.17	1.25	0.9103	1.50	0.64	3.50	0.5205
55 - 64	0.32	0.12	0.90	0.1671	1.23	0.52	2.93	0.8325
65+	0.33	0.11	1.02	0.2765	1.52	0.63	3.69	0.4930
Gender								
Female (Ref)								
Male	0.93	0.41	2.11	0.8656	0.95	0.54	1.66	0.8449
Census Region								
Midwest (Ref)								
Northeast	1.81	0.69	4.76	0.2796	0.85	0.24	2.94	0.4600
South	1.31	0.46	3.71	0.9883	1.27	0.40	3.99	0.5817
West	1.27	0.53	3.03	0.8795	1.29	0.45	3.64	0.4310
Hepatitis B & C Virus								
Negative (Ref)								
Positive	0.85	0.29	2.49	0.7693	0.86	0.34	2.18	0.7476
Charleson Comorbidity Index								
≤1 (Ref.)								
2	1.71	0.72	4.07	0.5303	1.42	0.69	2.91	0.5896
3+	4.66	2.06	10.54	0.0002	2.83	1.52	5.27	0.0015
Dual Eligibility Status								
No (Ref)								
Yes	1.17	0.56	2.47	0.6792	1.61	0.87	2.98	0.1288

PI: Protease Inhibitors, OR: Odds ratio, T2DM: Types II diabetes Mellitus, ART: Anti-Retroviral Therapy, CI: Confidence Interval

5. 3 Economic Burden of Comorbid T2DM

Section 5.3 describes the sample selection flow chart for study aim 3, baseline demographic and clinical characteristics of selected beneficiaries and the multivariate results of the impact of T2DM on different costs. The costs considered were total inpatient cost, total outpatient cost, total prescription cost, total OOP cost, total Medicare cost and total medical cost.

5.3.1 Flow chat for sample selection

Using 2013 to 2017 Medicare data with 1 million Medicare beneficiaries, we generated the study aim 3 sample in three steps. (Figure 5.4). First, we identified 2,627 beneficiaries with diagnosis of HIV/AIDS and 182,007 beneficiaries with diagnosis of T2DM. Second, we excluded a total of 181,488 beneficiaries, who have no record of HIV/AIDS diagnosis. Thus, leaving behind a total of 2,627 HIV/AIDS beneficiaries with or without T2DM diagnosis. Third, a total of 118 beneficiaries were exclude (1), if they either were enrolled in HMO plan or (2) if they were not continuously enrolled in Part A and B plan. A total of 2,509 HIV/AIDS positive beneficiaries were selected in the final sample or (3), if beneficiary have ESRD. The final sample consists of 498 HIV/AIDS positive beneficiaries with a diagnosis of T2DM (Case) and 2,011 HIV/AIDS positive beneficiaries without a diagnosis of T2DM.

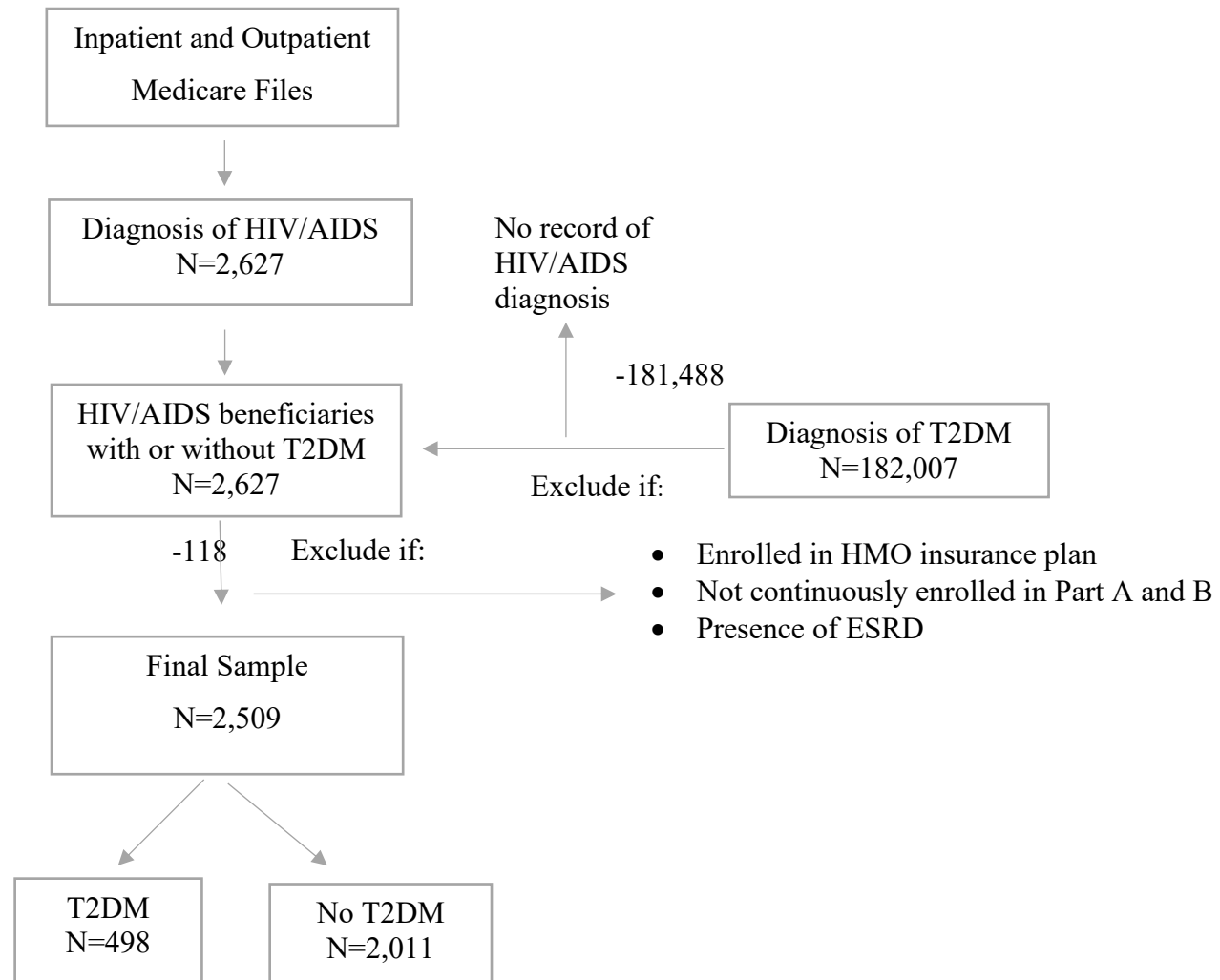


Figure 5.4 Sample selection flow chart for study aims 3

5.3.2 Descriptive analysis

Table 5.11 summarizes baseline characteristics of beneficiaries with HIV/AIDS, distinguishing between those with comorbid T2DM and those without comorbid T2DM. Except for hepatitis B and C variables, low income subsidy and dual eligibility variables, all other baseline characteristics were statistically significantly different between beneficiaries with a history of T2DM and those without. Beneficiaries in the T2DM history group and those in the non-T2DM history group are statistically significantly different in terms of age-group ($P=0.036$), gender; $p=0.015$, race category; $p=0.000$, region; $p=0.008$ and CCI scores, ($P<0.0001$). Beneficiaries with a history of T2DM and individuals without a history of T2DM are similar in terms of treatment with anti-retroviral drugs, hepatitis B/C virus, ($p=0.770$), and Medicare and Medicaid dual eligibility status ($p=0.312$).

Table 5.11. Baseline characteristics of HIV/AIDS positive beneficiaries with T2DM versus those without T2DM (N = 2,509)

	T2DM Status				
	T2DM (n=498)		Non-T2DM (n=2011)		P-Value
	N	%	N	%	
Treatment with ART					
Non-PIs	694	69.1	402	69.2	0.9549
PIs	311	30.95	179	30.8	
Age Group					
18 - 44 (Ref.)	18	3.6	97	4.8	0.0360
45 - 54	43	8.6	205	10.2	
55 - 64	116	23.3	556	27.7	
65+	321	64.5	1153	57.3	
Gender					
Male	340	68.3	1482	73.7	0.0150
Female	158	31.7	529	26.3	
Race					
Caucasian	188	37.8	970	48.2	0.0000
African America	265	53.2	874	167.0	
Other Race	45	9.0	43.46	8.3	
Census Region					
Midwest	77	15.5	341	17.0	0.0080
Northeast	117	23.5	447	22.3	
South	248	49.9	881	44.0	
West	55	11.1	333	16.6	
Hepatitis B & C Virus					
Negative	438	88.0	1759	87.5	0.7700
Positive	60	12.1	252	12.5	
Charlson Comorbidity Index					
0	88	17.7	387	19.2	<.0001
1	235	47.2	1184	58.9	
2	112	22.5	299	14.9	
3+	63	12.7	141	7.0	
Low Income Subsidy					
No	131	28.9	581	28.9	0.2520
Yes	367	73.7	1430	71.1	
Dual Eligibility Status					
No	133	26.7	583	29.0	0.3120
Yes	365	73.3	1428	71.0	

5.3.4 Average healthcare costs between beneficiaries with comorbid T2DM and those

without

Table 5.12 presents the unadjusted averages costs for different healthcare costs between HIV/AIDS positive beneficiaries with comorbid T2DM and those without. On average, the cost of hospitalization for individuals with comorbid T2DM was statistically significantly higher than the cost of hospitalization for individuals without comorbid T2DM: (mean diff.: 32, 622; 95 % CI: 26,329-38,915; $p < .0001$). The outpatient cost for individuals with a T2DM history was statistically significantly higher than in individuals without comorbid T2DM (mean diff.: 14, 894; 95 % CI: 11,402-18,385; $p < .0001$). Compared to individuals with comorbid T2DM, those without comorbid T2DM had statistically significantly higher Medicare costs. (mean diff.: 56,459; 95 % CI: 45,261-67,658; $p\text{-value} < .0001$). Beneficiaries with comorbid T2DM incur statistically significantly higher OOP costs than those without comorbid T2DM (mean diff.: 5,109; 95 % CI: 4,237-5,981; $p\text{-value} < .0001$). Prescription costs were statistically significantly higher for individuals with comorbid T2DM than those without (mean diff.: 17,974; 95 % CI: 9,301-26,648; $p < .0001$). Individuals with comorbid T2DM incurred higher overall total medical costs than individuals without comorbid T2DM (mean diff.: 65491; 95 % CI: 52,984-77,988); $p < .0001$).

Table 5.12. Average healthcare costs of HIV/AIDS positive beneficiaries with T2DM versus those without T2DM

	T2DM (n=496)	No T2DM (n=2011)				
	Mean ± Std	Mean ± Std	Mean Cost Difference	95 % CI		P- Value
Total hospitalization cost	57,628 ± 101,295	25,006 ± 53,882	32,622	26,329	38,915	<.0001
Total outpatient cost	26,600 ± 46,885	11,706 ± 36,436	14,894	11,402	18,385	<.0001
Total prescription drug cost	105,315 ± 114,061	87,341 ± 91,886	17,974	9,301	26,648	<.0001
Total Medicare cost	159,901 ± 158,736	103,442 ± 111,759	56,459	45,261	67,658	<.0001
Total OOP cost	9,976 ± 13,514	4,868 ± 789	5,109	4,237	5,981	<.0001
Total medical cost	189,543 ± 176,920	124,052 ± 125,048	65,491	52,984	77,988	<.0001

T2DM: Types II diabetes Mellitus, CI: Confidence Interval

5.3.5 Unadjusted GLM analysis of the impact of comorbid T2DM on healthcare costs

Table 5.13 shows the results of unadjusted GLM analysis with log link and gamma distribution, comparing different healthcare costs between individuals with comorbid T2DM and those without. We found that comorbid T2DM in HIV/AIDS is statistically significantly associated with a 73.19% $[(e^{0.54921}-1) * 100]$ increase in hospitalization costs ($p < .0001$) compared to individuals without T2DM on average. Compared to HIV/AIDS positive beneficiaries without T2DM, those with T2DM had 102.3 % $[(e^{0.7946}-1) * 100]$ higher total outpatient costs on average. ($P < .0001$) Compared to HIV/AIDS positive beneficiaries without T2DM, those with T2DM had 16.57 % $[(e^{0.1533}-1) * 100]$ higher prescription drug costs on average. ($p = 0.0023$). We also found that compared to HIV/AIDS positive beneficiaries without T2DM, those with T2DM had 103.24% $[(e^{0.7092}-1) * 100]$ higher total OOP costs on average. Considering total Medicare and total medical costs, compared to HIV/AIDS positive beneficiaries without T2DM, those with T2DM had 54.22% $[(e^{0.4332}-1) * 100]$ higher total Medicare costs and 52.53 % $[(e^{0.4222}-1) * 100]$ higher total medical costs on average.

Table 5.13 Unadjusted GLM analysis of the effect of comorbid T2DM on total healthcare costs

healthcare costs				
	Estimates	95 % CI		P-Value
Total Hospitalization Costs				
T2DM				
Negative (Ref)				
Positive	0.5492	0.4355	0.6630	<.0001
Total Outpatient Cost				
T2DM				
Negative (Ref)				
Positive	0.7946	0.6797	0.9094	<.0001
Total Prescription Drug Cost				
T2DM				
Negative (Ref)				
Positive	0.1533	0.0547	0.2519	0.0023
Total OOP Cost				
T2DM				
Negative (Ref)				
Positive	0.7092	0.6049	0.8135	<.0001
Total Medicare Cost				
T2DM				
Negative (Ref)				
Positive	0.4332	0.3405	0.5259	<.0001
Total Medical Cost				
T2DM				
Negative (Ref)				
Positive	0.4222	0.3330	0.5113	<.0001
GLM: Generalized Linear Model, T2DM: Types II diabetes Mellitus, CI: Confidence Interval				

5.3.6 Adjusted GLM analysis of effect of comorbid T2DM on different costs

Table 5.14 to tables 5:18 summarizes the multivariate GLM analysis of the impact of T2DM on different costs. GLM analysis controls for the baseline characteristics of the beneficiary such as: age-group, gender, region of the US, race category, CCI, Hepatitis B/C virus, low income subsidy and Medicare/Medicaid dual eligibility.

5.3.5.1 Total hospitalization costs

After controlling for potential confounders at the baseline in the GLM analysis (Table 5.14) the impact of T2DM on hospitalization was still statistically significantly higher in beneficiaries with T2DM compared to those without T2DM. We found that on average, HIV/AIDS positive beneficiaries with comorbid T2DM had a 63.34 % [$(e^{0.4907}-1) * 100$] increase in total hospitalization cost ($p < .0001$) compared to HIV/AIDS beneficiaries without comorbid T2DM.

Other covariates that are statistically significantly associated with changes in total hospitalization costs include race category, southern region, hepatitis B/C Virus, and CCI-1 categories. Compared to Caucasian beneficiaries with HIV/AIDS, African American HIV/AIDS positive beneficiaries had 39.98 % higher total hospitalization costs on average ($p < .0001$) while HIV/AIDS beneficiaries of 'other race' groups had 48.38 % higher total hospitalization costs on average ($p = 0.0023$). Compared to HIV/AIDS positive beneficiaries living in the Midwest region, those living in the Southern region had 16.48 % lower total hospitalization costs on average ($p = 0.0501$). Compared to HIV/AIDS beneficiaries without hepatitis B/C virus comorbidity, those with hepatitis B/C virus comorbidity had 40.78 % higher total hospitalization costs on average ($p < .0001$). Compared to HIV/AIDS beneficiaries without any comorbidity (CCI=0), those with a comorbidity of 1 (CCI=1) had 52.14 % lower total hospitalization costs on average ($p = 0.0054$).

Antiretroviral treatment with PIs did not significantly impact hospitalization cost compare to treatment with non-PIs. Compared to HIV/AIDS positive beneficiaries treated with non-PIs, those treated with PI had a 9.01 % lower total hospitalization cost on average, however, incremental cost was not statistically significant ($p = 0.2007$).

There was no statistically significant differences found in total hospitalization costs between: male and female beneficiaries ($p=0.5792$), those living in the Midwest and those living in the Northeast region ($p=0.8754$), and those living in Midwest and those living in the Western region ($p=0.1852$), between beneficiaries with CCI=0 and those with CCI=2 ($p=0.0857$), between beneficiaries with CCI=0 and those with CCI=3 ($p=0.9529$), and beneficiaries with dual eligibility and those without dual eligibility ($p=0.2007$).

Table 5.14 Adjusted GLM analysis of the effect of comorbid T2DM on total hospitalization costs

	Estimates	95 % CI		P-Value
Intercept	10.8392	10.2662	11.4121	<.0001
T2DM				
Negative (Ref)				
Positive	0.4907	0.3558	0.6256	<.0001
Treatment with ART				
Non-PIs (Ref)				
PIs	-0.0863	-0.2186	0.0459	0.2007
Age Group				
18 - 44 (Ref.)				
45 - 54	0.0473	-0.1651	0.2596	0.6626
55 - 64	0.0413	-0.1661	0.2486	0.6963
65+	0.1011	-0.1109	0.3132	0.3499
Gender				
Female (Ref)				
Male	-0.0408	-0.1851	0.1035	0.5792
Race				
Caucasian (Ref)				
African America	0.3363	0.1970	0.4756	<.0001
Other Race	0.3946	0.1409	0.6483	0.0023
Census Region				
Midwest (Ref)				
Northeast	-0.0162	-0.2187	0.1863	0.8754
South	-0.1801	-0.3603	0.0001	0.0501
West	0.1549	-0.0743	0.3842	0.1852
Hepatitis C Virus				
Negative (Ref)				
Positive	0.3420	0.1953	0.4888	<.0001
Charleson Comorbidity Index				
0 (Ref)				
1	-0.7368	-1.2556	-0.2180	0.0054
2	-0.4515	-0.9665	0.0634	0.0857
3+	0.0154	-0.4959	0.5267	0.9529
Dual Eligibility Status				
No				
Yes	0.0474	-0.1001	0.1948	0.5290

GLM: Generalized Linear Model, T2DM: Types II diabetes Mellitus, CI: Confidence Interval, PI: Protease Inhibitor, ART: Antiretroviral Therapy

5.3.5.2 Total outpatient costs

After controlling for potential confounders at the baseline in the GLM analysis (Table 5.15) the impact of T2DM on total outpatient cost was still statistically significantly higher among beneficiaries with comorbid T2DM than to those without comorbid T2DM. Results further show that, on average, HIV/AIDS positive beneficiaries with comorbid T2DM had a 50.26% [$(e^{0.4072}-1) * 100$] increase in total outpatient cost ($p < .0001$) compared to HIV/AIDS beneficiaries without comorbid T2DM .

Other covariates that are statistically significantly associated with changes in total outpatient cost include age group (45-54), race, region and CCI. Compared to HIV/AIDS positive beneficiaries living in the Midwestern region, those living in the Northeast region had a 27.10 % lower total outpatient cost on average ($p=0.0195$). The Southern region had 25.01 % lower total outpatient costs on average ($p=0.0187$), and the Western region had 26.35 % lower total outpatient costs on average ($p=0.0359$). Compared to HIV/AIDS beneficiaries without any comorbidity (CCI=0), those with a comorbidity of: CCI=1 had 59.94 % higher total outpatient costs on average ($p=0.0045$), CCI=2 had 243.36 % higher total outpatient costs on average ($p < .0001$), and CCI=3+ had 577.34 % higher total outpatient cost on average ($p < .0001$).

Antiretroviral treatment with PIs did not significantly impact outpatient cost compare to treatment with non-PIs. Compared to HIV/AIDS positive beneficiaries treated with non-PIs, those treated with PI had a 4.24 % higher total outpatient cost on average, however, incremental cost was not statistically significant ($p=0.5265$). There was no statistically significant difference in changes in total outpatient cost between: age groups, male and female beneficiaries ($p=0.0662$), and beneficiaries with dual eligibility and those without dual eligibility ($p=0.3379$).

Table 5.15 Adjusted GLM analysis of the effect of comorbid T2DM on total outpatient costs

	Estimates	95 % CI		P-Value
Intercept	8.3138	7.9020	8.7256	<.0001
T2DM				
Negative (Ref)				
Positive	0.4072	0.2677	0.5467	<.0001
Treatment with ART				
Non-PIs (Ref)				
PIs	0.0415	-0.0869	0.1698	0.5265
Age Group				
18 - 44 (Ref.)				
45 - 54	0.2322	0.0242	0.4403	0.0287
55 - 64	0.1896	-0.0084	0.3877	0.0605
65+	0.1380	-0.0690	0.3450	0.1913
Gender				
Female (Ref)				
Male	-0.0810	-0.2228	0.0607	0.2625
Race				
Caucasian (Ref)				
African America	0.1074	-0.0352	0.2499	0.1399
Other Race	-0.1883	-0.4228	0.0462	0.1155
Census Region				
Midwest (Ref)				
Northeast	-0.2398	-0.4411	-0.0385	0.0195
South	-0.2232	-0.4092	-0.0372	0.0187
West	-0.2339	-0.4524	-0.0154	0.0359
Hepatitis C Virus				
Negative (Ref)				
Positive	0.0708	-0.0821	0.2237	0.3641
Charlson Comorbidity Index				
0 (Ref)				
1	0.4696	0.1453	0.7939	0.0045
2	1.2336	0.9051	1.5621	<.0001
3+	1.9130	1.5811	2.2450	<.0001
Dual Eligibility Status				
No				
Yes	-0.0704	-0.2144	0.0736	0.3379

GLM: Generalized Linear Model, T2DM: Types II diabetes Mellitus, CI: Confidence Interval, PI: Protease Inhibitor, ART: Antiretroviral Therapy

5.3.5.3 Total OOP

After controlling for potential confounders at the baseline in the GLM analysis (Table 5.16) the impact of T2DM on total OOP cost was still statistically significantly higher among beneficiaries with comorbid T2DM compared to those without comorbid T2DM. Results show that on average, HIV/AIDS positive beneficiaries with comorbid T2DM had a 59.15% [$(e^{0.4647}-1) * 100$] increase in total OOP cost ($p < .0001$) compared to HIV/AIDS beneficiaries without comorbid T2DM.

Other covariates statistically significantly associated with changes in total OOP cost include race, hepatitis B/C Virus and CCI characteristics. Compared to Caucasian beneficiaries with HIV/AIDS, beneficiaries of 'other race' group had 44.40 % lower total OOP costs on average ($p = 0.0009$). Compared to HIV/AIDS beneficiaries without hepatitis B/C virus comorbidity, those with hepatitis B/C virus comorbidity had 32.14 % higher total OOP costs on average ($p < 0.0001$). Compared to HIV/AIDS beneficiaries without any comorbidity (CCI=0), those with a comorbidity of: CCI=1 had 36.15 % higher total OOP costs on average ($p = 0.0466$), CCI=2 had 119.88 % higher outpatient costs on average ($p < .0001$), and CCI=3+ had 274.75 % higher OOP costs on average ($p < .0001$).

Antiretroviral treatment with PIs did not significantly impact OOP cost compare to treatment with non-PIs. Compared to HIV/AIDS positive beneficiaries treated with non-PIs, those treated with PI had a 6.97 % higher total OOP cost on average, however, incremental cost was not statistically significant ($p = 0.2590$). We also found that there was no statistically significant difference in changes to total OOP costs between: age groups, region, male and female beneficiaries ($p = 0.0843$), and those without dual eligibility ($p = 0.8332$).

Table 5.16 Adjusted GLM analysis of the effect of comorbid T2DM on total OOP costs

	Estimates	95 % CI		P-Value
Intercept	7.9091	7.5290	8.2892	<.0001
T2DM				
Negative (Ref)				
Positive	0.4647	0.3366	0.5929	<.0001
Treatment with ART				
Non-PIs (Ref)				
PIs	0.0674	-0.0496	0.1844	0.2590
Age Group				
18 - 44 (Ref.)				
45 - 54	0.1357	-0.3261	0.2548	0.1628
55 - 64	0.1479	-0.3318	0.3359	0.1147
65+	0.1788	-0.2713	0.3734	0.4221
Gender				
Female (Ref)				
Male	-0.0113	-0.1403	0.1177	0.8635
Race				
Caucasian (Ref)				
African America	-0.0182	-0.1444	0.1080	0.7774
Other Race	-0.3674	-0.5836	-0.1512	0.0009
Census Region				
Midwest (Ref)				
Northeast	-0.1409	-0.3230	0.0411	0.1292
South	-0.0921	-0.2554	0.0712	0.2691
West	-0.1182	-0.3187	0.0823	0.2478
Hepatitis C Virus				
Negative (Ref)				
Positive	0.2787	0.1387	0.4186	<.0001
Charlson Comorbidity Index				
0 (Ref)				
1	0.3086	0.0046	0.6125	0.0466
2	0.7879	0.4810	1.0949	<.0001
3+	1.3211	1.0121	1.6301	<.0001
Dual Eligibility Status				
No				
Yes	-0.0578	-0.1909	0.0753	0.3945

GLM: Generalized Linear Model, T2DM: Types II diabetes Mellitus, CI: Confidence Interval, PI: Protease Inhibitor, ART: Antiretroviral Therapy, OOP: out of Pocket Cost

5.3.5.4 Total prescription cost

After controlling for potential confounders at the baseline in the GLM analysis (Table 5.17) the difference in total prescription costs between individuals with comorbid T2DM and those without comorbid T2DM was no longer statistically significant. We found that compared to HIV/AIDS beneficiaries without comorbid T2DM, those with T2DM had 6.97 % $[(e^{0.0674}-1) * 100]$ higher total prescription costs on average, however, the incremental cost was not statistically significant. ($p=0.3113$).

Other covariates statistically significantly associated with changes in total prescription drug cost include hepatitis B/C and CCI. Compared to HIV/AIDS positive beneficiaries without hepatitis B/C, those diagnosed with hepatitis B/C had 21.12 % higher total prescription costs on average ($p=0.0076$). Compared to HIV/AIDS beneficiaries without any comorbidity (CCI=0), those with a comorbidity of: CCI=1 had 140.37 % higher total prescription costs on average ($p<.0001$), CCI=2 had 223.88 % higher total prescription costs on average ($p<.0001$), CCI=3+ had 255.41 % higher total prescription costs on average ($p<.0001$).

Antiretroviral treatment with PIs did not significantly impact prescription drug cost compare to treatment with non-PIs. Compared to HIV/AIDS positive beneficiaries treated with non-PIs, those treated with PI had a 4.29 % higher total prescription drug cost on average, however, incremental cost was not statistically significant ($p=0.4728$). We also found that there was no statistically significant difference in changes to total prescription costs between: race, census region, hepatitis B/C ($p=0.1251$) or beneficiaries with dual eligibility versus those without dual eligibility ($p=0.9318$).

Table 5.17 Adjusted GLM analysis of impact of T2DM on total prescription drug costs

	Estimates	95 % CI		P-Value
Intercept	10.2656	9.8838	10.6474	<.0001
T2DM				
Negative (Ref)				
Positive	0.0674	-0.0631	0.1978	0.3113
Treatment with ART				
Non-PIs (Ref)				
PIs	0.0420	-0.0727	0.1567	0.4728
Age Group				
18 - 44 (Ref.)				
45 - 54	0.0340	-0.1480	0.2161	0.7141
55 - 64	0.0950	-0.0827	0.2727	0.2947
65+	0.1517	-0.2364	0.3330	0.5834
Gender				
Female (Ref)				
Male	0.1075	-0.0206	0.2355	0.1000
Race				
Caucasian (Ref)				
African America	-0.0650	-0.1873	0.0572	0.2972
Other Race	-0.0759	-0.2876	0.1358	0.4823
Census Region				
Midwest (Ref)				
Northeast	0.0703	-0.1051	0.2458	0.4321
South	-0.0398	-0.1960	0.1165	0.6178
West	0.1241	-0.0736	0.3219	0.2186
Hepatitis C Virus				
Negative (Ref)				
Positive	0.1916	0.0510	0.3323	0.0076
Charlson Comorbidity Index				
0 (Ref)				
1	0.8770	0.5654	1.1886	<.0001
2	1.1752	0.8610	1.4895	<.0001
3+	1.2681	0.9512	1.5851	<.0001
Dual Eligibility Status				
No				
Yes	0.0274	-0.0994	0.1541	0.6723

GLM: Generalized Linear Model, T2DM: Types II diabetes Mellitus, CI: Confidence Interval, PI: Protease Inhibitor, ART: Antiretroviral Therapy

5.3.5.5 Total Medicare cost

After controlling for potential confounders at the baseline in the GLM analysis (Table 5.18) the impact of T2DM on total Medicare cost was still statistically significantly higher among beneficiaries with comorbid T2DM compared to those without comorbid T2DM. Result show that compared to HIV/AIDS beneficiaries without comorbid T2DM, those with comorbid T2DM had 27.95 % $[(e^{0.2465}-1) * 100]$ higher total Medicare costs on average ($p < .0001$).

Other covariates statistically significantly associated with changes in total Medicare cost include hepatitis B/C Virus and CCI characteristics. Compared to HIV/AIDS beneficiaries without hepatitis B/C virus comorbidity, those with hepatitis B/C virus comorbidity had 29.15 % higher total Medicare costs on average ($p < .0001$). Compared to HIV/AIDS beneficiaries without any comorbidity (CCI=0), those with comorbidity of: CCI=1 had 93.00 % higher total Medicare costs on average ($p < .0001$), CCI=2 had 189.33 % higher total Medicare cost on average ($p < .0001$), CCI=3+ had 309.68 % higher total Medicare cost on average ($p < .0001$).

Antiretroviral treatment with PIs did not significantly impact Medicare cost compare to treatment with non-PIs. Compared to HIV/AIDS positive beneficiaries treated with non-PIs, those treated with PI had a 2.80 % higher total Medicare cost on average, however, incremental cost was not statistically significant ($p = 0.6036$). Also, there was no statistically significant difference in changes to total Medicare cost between: age, race, region, male and female beneficiaries ($p = 0.5089$) or beneficiaries with dual eligibility and those without dual eligibility ($p = 0.9611$).

Table 5.18 Adjusted GLM analysis of impact of T2DM on total Medicare costs

	Estimates	95 % CI		P-Value
Intercept	10.4320	10.0895	10.7744	<.0001
T2DM				
Negative (Ref)				
Positive	0.2465	0.1294	0.3636	<.0001
Treatment with ART				
Non-PIs (Ref)				
PIs	0.0276	-0.0765	0.1316	0.6036
Age Group				
18 - 44 (Ref.)				
45 - 54	0.0341	-0.1336	0.2018	0.6900
55 - 64	0.0786	-0.0848	0.2420	0.3456
65+	0.0962	-0.0762	0.1638	0.9430
Gender				
Female (Ref)				
Male	0.0393	-0.0772	0.1558	0.5089
Race				
Caucasian (Ref)				
African America	0.0524	-0.0588	0.1636	0.3559
Other Race	0.0129	-0.1802	0.2060	0.8956
Census Region				
Midwest (Ref)				
Northeast	-0.0019	-0.1625	0.1587	0.9815
South	-0.0809	-0.2243	0.0625	0.2691
West	0.1022	-0.0769	0.2813	0.2633
Hepatitis C Virus				
Negative (Ref)				
Positive	0.2558	0.1290	0.3826	<.0001
Charleson Comorbidity Index				
0 (Ref)				
1	0.6575	0.3831	0.9318	<.0001
2	1.0624	0.7859	1.3388	<.0001
3+	1.4102	1.1332	1.6872	<.0001
Dual Eligibility Status				
No				
Yes	-0.0029	-0.1199	0.1141	0.9611

GLM: Generalized Linear Model, T2DM: Types II diabetes Mellitus, CI: Confidence Interval, PI: Protease Inhibitor, ART: Antiretroviral Therapy

5.3.5.6 Total medical cost

After controlling for potential confounders at the baseline in the GLM analysis (Table 5.19) the impact of comorbid T2DM on total medical costs was still statistically significantly higher among beneficiaries with comorbid T2DM compared to those without comorbid T2DM. Results show that compared to HIV/AIDS beneficiaries without comorbid of T2DM, those with comorbid T2DM had 27.82 % [$(e^{0.2455}-1) * 100$] higher total medical costs on average ($p < .0001$).

Other covariates statistically significantly associated with changes in total medical costs include hepatitis B/C Virus and CCI characteristics. Compared to HIV/AIDS beneficiaries without hepatitis B/C virus comorbidity, those with hepatitis B/C virus comorbidity had 27.21 % higher total medical costs on average ($p = 0.0001$). Compared to HIV/AIDS beneficiaries without any comorbidity (CCI=0), those with a comorbidity of: CCI=1 had 92.97 % higher total medical costs on average ($p < .0001$), CCI=2 had 185.68 % higher total medical costs on average ($p < .0001$), CCI=3+ had 289.00 % higher total medical costs on average ($p < .0001$).

Antiretroviral treatment with PIs did not significantly impact total medical cost compared to treatment with non-PIs. Compared to HIV/AIDS positive beneficiaries treated with non-PIs, those treated with PI had a 2.93 % higher total medical cost on average, however, incremental cost was not statistically significant ($p = 0.5706$). No statistically significant difference was found in the changes to total medical cost between male and female beneficiaries ($p = 0.3729$), age category, race category, gender, region, and dual eligibility versus those without dual eligibility ($p = 0.8912$).

Table 5.19 Adjusted GLM analysis of impact of T2DM on total medical costs

	Estimates	95 % CI		P-Value
Intercept	10.6445	10.3171	10.9718	<.0001
T2DM				
Negative (Ref)				
Positive	0.2455	0.1334	0.3577	<.0001
Treatment with ART				
Non-PIs (Ref)				
PIs	0.0289	-0.0710	0.1289	0.5706
Age Group				
18 - 44 (Ref.)				
45 - 54	0.0078	-0.1532	0.1687	0.9246
55 - 64	0.0522	-0.1047	0.2090	0.5146
65+	0.0758	-0.1691	0.2575	0.9444
Gender				
Female (Ref)				
Male	0.0526	-0.0589	0.1642	0.3552
Race				
Caucasian (Ref)				
African America	0.0661	-0.0406	0.1727	0.2248
Other Race	-0.0014	-0.1862	0.1833	0.9877
Census Region				
Midwest (Ref)				
Northeast	-0.0175	-0.1721	0.1371	0.8244
South	-0.1029	-0.2409	0.0351	0.1440
West	0.0727	-0.0995	0.2450	0.4077
Hepatitis C Virus				
Negative (Ref)				
Positive	0.2407	0.1189	0.3625	0.0001
Charlson Comorbidity Index				
0 (Ref)				
1	0.6574	0.3957	0.9191	<.0001
2	1.0497	0.7858	1.3137	<.0001
3+	1.3584	1.0937	1.6230	<.0001
Dual Eligibility Status				
No				
Yes	0.0078	-0.1041	0.1198	0.8912

GLM: Generalized Linear Model, T2DM: Types II diabetes Mellitus, CI: Confidence Interval, PI: Protease Inhibitor, ART: Antiretroviral Therapy

5.4 Sensitivity Analysis

The use of the PS matching approach in study aim 1 and 2 included only matched beneficiaries in the analytical sample and excluded unmatched beneficiaries, which may substantially impact the main results. To evaluate the sensitivity of these exclusions on the results, adjusted logistic regressions were re-fitted using the inverse probability-of-treatment weighting (IPTW) (instead of matching) which is a type of PS analytical method that uses complete samples in the analysis. This section presents the summary of the results of the sensitivity analysis of treatment with PI and the odds of developing T2DM, and the race sub-group analysis of these effects. (Table 5.20). The results of sensitivity analysis are consisted with the main results based on PS matching approach in terms magnitude and direction of association.

Compared to beneficiaries treated with non-PIs, those treated with PIs were shown to be 69% more likely to develop T2DM after adjusting for covariates (OR=1.69; 95% CI: 1.42-2.01). (Table 5.20). Compared to beneficiaries who are not treated with ART, those treated with PIs were 73% more likely to develop T2DM after adjusting for covariates (OR=1.73; 95% CI: 1.46-2.05).

Considering race sub-group results, among Caucasian beneficiaries, it was found that compared to Caucasian beneficiaries treated with non-PI, those treated with PIs were 1.70 times more likely to develop T2DM after adjusting for covariates (OR=1.70; 95% CI: 1.30-2.22). Odds of developing T2DM among Caucasian beneficiaries who were treated with PI were 2.05 times higher than the odds of developing T2DM in Caucasian beneficiaries who were not treated with ART, after adjusting for covariates (OR=2.05; 95% CI: 1.52-2.77). We found that odds of developing T2DM among African American beneficiaries treated with PI were 2.17 times higher than odds of developing T2DM in African American beneficiaries

treated with non-PI. (OR=2.17; 95% CI: 1.71 -2.76). Odds of developing T2DM among African American beneficiaries treated with PI were 2.20 times higher than the odds of developing T2DM in African American beneficiaries who were not treated with ART. (OR=2.20; 95% CI: 1.74 -2.79).

Table 5.20 Sensitivity analysis: Adjusted logistic regression analysis of factors associated with development of T2DM

	AOR	95 % CI		P-Value
Medication Exposure				
Non-PIs (Ref)				
PIs	1.69	1.42	2.01	<.0001
Medication Exposure				
No-ART (Ref)				
PIs	1.73	1.46	2.05	<.0001
Caucasians Sub-groups				
Medication Exposure				
Non-PIs (Ref)				
PIs	1.70	1.30	2.22	0.0001
Medication Exposure				
No-ART (Ref)				
PIs	2.05	1.52	2.77	<.0001
African Americans Sub-groups				
Medication Exposure				
Non-PIs (Ref)				
PIs	2.17	1.71	2.76	<.0001
Medication Exposure				
No-ART (Ref)				
PIs	2.20	1.74	2.79	<.0001

PI: Protease Inhibitors, AOR: Adjusted Odds ratio, T2DM: Types II diabetes Mellitus, ART: Anti-Retroviral Therapy, CI: Confidence Interval

CHAPTER 6

DISCUSSION

This chapter presents the discussion of all results in the context of existing evidence and presents the significance, innovation, strengths and limitations of this dissertation.

6.1 Treatment with PI and Development of T2DM

One of the objectives of this dissertation is to assess the association between PIs use and incidences of T2DM comparing beneficiaries in both therapy group pairs- PIs versus non-PIs and PIs verse no-ART therapy groups. We compared PIs versus non-PIs therapy groups and found that among Medicare beneficiaries diagnosed with HIV/AIDS, beneficiaries treated with PIs had higher adjusted odds of developing T2DM compared to beneficiaries treated with non-PIs. Although this study reports evidence among the population of Medicare recipients, our results are similar to the findings in some previous studies which examined subjects sampled from other populations. Studies conducted by Capeau *et al.*, in France analyzed medical records of a cohort of 1,046 patients followed over a 10-year period. Conclusions showed that short term exposure to indinavir was associated with increased incidences of T2DM ⁷⁴, which is similar to the increased odds of developing T2DM found in this study. Similarly, Ledergerber *et al* followed 6,513 HIV patients over a six year analytical period and found that the use of PIs based RTIs were associated with an increased risk of T2DM. ¹⁰⁰ Studies conducted by both Tsiodras

et al. and Hughes *et al.* demonstrated that use of PI was independently associated with elevated hyperglycemia and an increase in development of T2DM, respectively.^{102,103} A 2-fold increase (two-fold (AOR: 1.52) in the odds of developing T2DM in Hughes *et al.*¹⁰³ is similar to the two-fold (AOR: 1.74) increase found in this study.

This study incorporated non-PIs groups as a control group (mainly the NNRTIs and NRTIs) when assessing association between T2DM and PIs use, which is similar to the control group used in Justman *et al.*¹⁰⁴ Justman and his colleagues analyzed the risk of diabetes in a cohort of 1,785 non-pregnant HIV positive women treated with PIs versus those treated with RTIs.¹⁰⁴ After a four-year follow-up, they found that patients treated with PIs had an increase in incidences of diabetes compare to RTI users, which is similar to the findings of this study.¹⁰⁴ Our result is similar to findings from a previous study which incorporated a PI naïve group as a control group. Carr *et al.* compared PIs with PIs naïve HIV patients after 2-years of follow-up and found that hyperlipidemia and impaired glucose were significantly common among PI users compared to PI-naïve HIV patients.¹⁰⁵ Given that subjects in the PI-naïve control group in Carr *et al* were exposed to other ARTs just as the non-PI control group in this study, our findings corroborates the findings of Carr *et al.*

Although this study demonstrates an association of treatment with PIs and increased odds of developing T2DM within the Medicare population, our result is similar to Tripathi *et al.* which analyzed South Carolina Medicaid HIV/AIDS population. They found that cumulative exposure to protease inhibitors are significantly associated with a higher risk of diabetes among the South Carolina Medicaid population.¹⁰⁸ Evidence from Tripathi *et al.* can only be generalized to South Carolina Medicaid recipients and cannot

be extended to the national level. However, since similar evidence exists in the Medicare population as we found in this study, it could be hypothesized that the treatment with PI may be associated with an increased risk of developing diabetes within the national Medicaid HIV/AIDS population as well, just as the national Medicare population in this study. Future studies should focus on analyzing national Medicaid beneficiaries with HIV/AIDS in order to provide evidence on both national Medicare and Medicaid populations. This will help the CMS in developing a risk management approach for clinical management of HIV in both Medicaid and Medicare beneficiaries when using PIs.

This study incorporated no-ARTs as a control group and directly compared PIs versus no-ART therapy groups. Results based on this therapy group pair shows the extent to which the odds of developing T2DM could vary between individuals treated with PIs versus those who were not treated with any ART, which, at best, provides a clear-cut estimate of association of PIs and T2DM. None of the published studies that reported association between PIs and increased incidences of T2DM incorporated or directly compared a no-ART group as a control group with a PIs group when estimating the risk of T2DM. In this study, we found that among Medicare beneficiaries diagnosed with HIV/AIDS, those treated with PIs had higher adjusted odds of developing T2DM compared to beneficiaries not treated with ARTs. In Justman *et al*, RTIs were incorporated as a control group for comparison pairs – RTI versus PI and RTI versus no-ART comparison pairs.¹⁰⁴ In RTIs versus no-ART, they found an increasing risk of T2DM among the RTI groups compared to no-ART, although the result was not statistically significant.¹⁰⁴ In RTI versus PI comparison pair, they found increasing risk in

PI compared to RTI groups. While RTI versus no-ART comparison is not similar to the PI versus no-ART used in this study, it could be carefully deduced from Justman *et al* that a PIs versus no-ART comparison may show in increasing risk of developing T2DM if it was compared in their study.

This study analyzed the odds of developing T2DM between a PIs versus non-PIs group and PIs versus no-ARTs group and found increased odds of developing T2DM in PIs versus non-PIs (AOR: 1.74) and PI versus no-ART groups (AOR: 1.83), respectively. As expected, the odds of developing T2DM is higher in the no-ARTs comparison group than in the non-PIs comparison group. Given that previous studies had shown that the use of RTIs are association with an increased risk of developing T2DM^{121-123,174}, thus individuals in the PIs versus non-PIs comparison groups have T2DM risks higher than the baseline risk. Hence, comparing PIs versus non-PIs would results to a smaller odds ratio than in PI versus no-ART (the probability of T2DM in PI group/ divided by the probability of T2DM in non-PIs group). On the other hand, the T2DM risk in the no-ART arm are generally the baseline T2DM risk and much smaller than the risk of T2DM in the PIs arm, thus comparison of PIs versus no-ARTs will result to a larger odds ratio (probability of T2DM in PI group divided by the probability of T2DM in non-PIs group) than in PIs versus no-ARTs comparison.

6.2 Race Sub-group Analysis of PI Use and Development of T2DM

This study is the first to report racial disparities in odds of developing T2DM among patients treated with PIs. We examined racial disparities in odds of developing T2DM comparing beneficiaries treated with PIs versus those treated with non-PIs, and comparing beneficiaries treated with PIs versus those not treated with ARTs.

In the PIs versus non-PIs comparison groups, we found that African American beneficiaries treated with PI had higher odds of developing T2DM compared to African American beneficiaries treated with non-PIs. We also found that Caucasian beneficiaries treated with PIs had higher odds of developing T2DM compared to Caucasian beneficiaries treated with non-PI. The odds of developing T2DM was higher in African American race-subgroup (OR=2.09) compared to the odds among Caucasian race-subgroup (OR=1.90). This finding agrees with our hypothesis which states that in comparing PIs and non-PIs therapy group, the odds of developing T2DM after PIs use is higher among African American race compared to the odds of developing T2DM after PIs use among the Caucasian beneficiaries.

In the PI versus no-ART comparison groups, we found that African American beneficiaries treated with PI had higher odds of developing T2DM compared to African American beneficiaries who were not treated with ARTs. We also found that Caucasian beneficiaries treated with PIs had higher odds of developing T2DM compared to Caucasian beneficiaries not treated with ART. Again, we found that the odds of developing T2DM was higher in African American race-subgroup (OR=2.39) compared to the odds among Caucasian race-subgroup (OR=1.86). These findings agree with our hypothesis which states that in comparing PIs and no-ARTs therapy group, the odds of developing T2DM after PIs use are higher among African American race compared to the odds of developing T2DM after PIs use among the Caucasian beneficiaries.

In the analysis of each therapy group pairs, our study demonstrates that use of PIs is associated with higher odds of developing T2DM in both race subgroups. Specifically, treatment with PIs was associated with development of T2DM in both African American

and Caucasian Medicare beneficiaries with HIV/AIDS infection. However, we found that the impact was higher in one race sub-group than the other. This study reports that the odds of developing T2DM was higher in African Americans treated with PIs compared to Caucasians treated with PIs.

Previous racial disparities studies had reported that African Americans have higher prevalence of T2DM compare to Caucasians. According to the CDC, African American and other racial and ethnic minority populations remain at higher risk for incident T2DM and its complications.¹⁷⁵ However, recent studies by Bancks *et al* suggested that African Americans and Caucasians actually have the same biological risk of developing T2DM.¹⁷⁶ They concluded that the there is no racial disparities in risk of developing T2DM after accounting for various modifiable risk factors such as family history of diabetes, racial segregation, tract-level poverty, depressive symptoms, family education, current employment, alcohol consumption, and smoking rather than genetic factors.¹⁷⁶ The difference in odds of developing T2DM between African Americans and Caucasians in our study could result from some of the underlying factors which were not controlled for in this study. Factors such as family history of diabetes, depressive symptoms, education, employment and behavioral factors such as alcohol consumption and smoking.

6.3 Economic Burden of Comorbid T2DM

This study is the first to evaluate the national economic burden of comorbid T2DM in HIV/AIDS. We found that compared to HIV/AIDS positive beneficiaries without comorbid T2DM, those with comorbid T2DM had higher total hospitalization cost, higher total outpatient cost, higher total OOP costs, higher total Medicare cost and

higher total medical cost on average. Conversely, this study did not detect a significant difference in total cost of prescription drugs between beneficiaries with history of T2DM and those without. Except for total cost of prescription drugs, the findings of this study are similar to our hypothesis for all other health costs.

This finding is in tandem with the study conducted by Zingmond *et al* which described the comorbidities in people living with HIV/AIDS in relation to hospitalization, inpatient and prescription drug costs.⁷ They reported that among California Medicare beneficiaries with HIV/AIDS, comorbidity is associated with increase in median inpatient costs and outpatient costs paid by the Medicare and patients.⁷ Given the clinical breakthrough in HIV/AIDS management since advent of ARTs which includes decreasing hospitalization rates and ambulatory care for HIV/AIDS patients, hospitalization is now largely due to non-HIV/AIDS comorbidities, infections and complications.¹⁷⁷ Approximately 71 % of deaths among hospitalized HIV/AIDS patients is attributed to non-HIV related conditions such as other infections and various chronic diseases.¹⁷⁷ In other words, comorbidities itself has a significant impact on mortality rate among hospitalized patients with HIV/AIDS as well as total hospitalization cost paid by patients and their insurance providers. Thus, the total hospitalization costs, outpatient costs, OOP costs, total Medicare costs and total medical costs is expected to be sensitive to comorbid T2DM as found in this study.

In contrast to the sensitivity of these costs to comorbid T2DM, we found that prescription drug cost is insensitive to comorbid T2DM. Prescription drug cost is not sensitive to comorbid T2DM because the high cost of ARTs outweighs the cost of anti-diabetes drugs, and so the total cost of anti-diabetes drugs would not make a significant

difference in terms of total prescription drug costs for HIV/AIDS patients. This finding is in tandem with the study conducted by Zingmond *et al* which found that ARTs constitute the largest share of cost of care for HIV patients and suggested that because ARTs are more expensive than medication for other comorbidities, comorbidities would have no significant impact on cost of prescription for patients with HIV/AIDS which outweighs medication costs for other conditions. ⁷

6.4 Sensitivity Analysis

We performed a sensitivity analysis using IPTW approach to evaluate the sensitivity of excluding unmatched beneficiaries on the results of study aim 1 and 2 using adjusted logistic regressions. We found that the sensitivity analysis results were similar to the main result in aim 1 and 2 in terms of between group associations and direction of associations. Analysis of the PS matched sample in this study is not sensitive to the exclusion of unmatched samples.

6.5 Innovation

This study is innovative in the following three important areas. To begin with, it is the first study of its kind to examine the odds of developing T2DM following PIs use among Medicare beneficiaries diagnosed with HIV/AIDS. Second, the most recent Medicare data (2012-2017) was used for this study enabling the evaluation of the odds of T2DM using current and recent FDA approved ARTs and generate the most current evidence. No previous studies in the current literature have examined this topic. Third, this study is the first to determine racial disparity in the odds of developing T2DM following PI use among Medicare beneficiaries with HIV/AIDS. No previous studies

have examined the race/ethnicity disparity in the odds of developing T2DM among Medicare beneficiaries with HIV in current literature. Fourth, this study is the first of its kind to explore the economic burden of comorbid T2DM among the HIV/AIDS positive Medicare population. The evidence generated by this study is the first and the most current national economic burden with estimates that are adjusted to the 2017 dollar. No previous studies have examined the national economic burden of comorbid T2DM.

6.6 Limitations

Several data and study design related limitations may exist in this study. This study is a non-randomized observational study. Although we used PS matching approach to account for potential selection bias due to non-randomization into therapy groups. However, only the beneficiary characteristics available in the Medicare data were used for the PS matching. Also, as a limitation of the PS matching approach, it is unable to account for unmeasured confounders that could have impacted the results of this study. The study aim 3 used cross-sectional study design to analyze economic burden of T2DM on health care costs however, this study design could not establish causality of association. Thus, the change in healthcare cost between beneficiaries with T2DM and those without cannot be causally attributed to T2DM in this study.

Some data related limitations have been noted. Several potential confounders were not observed in this study and thus were not controlled for. Medicare data has limited information on risk factors of diabetes including physical activities of the beneficiaries, a family history of diabetes, diets and other lifestyle behaviors. The Medicare database does not have vital HIV related clinical information such as CD4 count and viral load information of the beneficiaries, which is a very important

determinant of the type ART prescribed. As a secondary data which is originally collected for administrative and billing purposes rather than for this study, and of which data collection were not under the control of the investigators of this study, we suspect a potential information bias consequently.

CHAPTER 7

CONCLUSION

This study found that use of PIs in HIV/AIDS positive Medicare beneficiaries may be associated with higher odds of developing T2DM than those who were managed with non-PIs and higher than those who were not treated with ARTs. These findings are consistent within both African American and Caucasian race sub-groups. However, African American race-subgroup had higher odds of developing T2DM in both PI versus no-ART and PI-versus non-PI comparison pairs than the odds among the Caucasian race-subgroup. Furthermore, this study found that HIV/AIDS Medicare beneficiaries with a history of T2DM have higher total hospitalization costs, total outpatient costs, total OOP costs, total Medicare costs and total medical costs than HIV/AIDS positive beneficiaries without a history of T2DM

This study presents three policy impacting significances. First, in the light of the controversies regarding safety and tolerability of PIs, a clinical risk management approach is a necessity when treating the elderly and the Medicare beneficiaries who have HIV/AIDS. This becomes important because treatment of HIV infection and consequently creating or exacerbating the onset of another condition, such as T2DM, is a huge concern to clinicians, the Medicare system, and patients. As a preventable adverse event, the findings of this study will guide clinicians and infectious disease experts in preventing this adverse effect by making evidence-based risk management decisions in

the clinical use of PIs among the Medicare population with HIV/AIDS. Evidence-based risk management approach will help avoid HIV treatment related T2DM in this population, who are already enormously predisposed.

Second, racial/ethnic variations in HIV/AIDS epidemiology and treatment has been established. As a vulnerable population with less HIV-care and attention, evidence of racial/ethnic disparity in the odds of developing T2DM following PIs use is key in ensuring proper risk management across race sub-groups. The findings of our study suggest that while the odds of developing T2DM is consistent in both African American and Caucasian race sub-groups, the odds were higher in African Americans than in Caucasians. Our study suggests that personalized medicine should be considered when planning clinical risk management approach for use of PIs with a consideration for the race-subgroup in whom risks of T2DM are higher.

The increasing population of Medicare beneficiaries with HIV, who are at higher risk for T2DM, suggests an increasing population of HIV positive beneficiaries with comorbid T2DM. This may pose a significant economic burden on the Medicare system, which is already the largest source of Federal spending for HIV care. As the population ages and life expectancies increase, Medicare plans to continue to play an increasingly significant role in HIV care, which is why it is important to understand the economic burden of comorbid T2DM. Given the growing aging population and increasing per capita costs for HIV positive beneficiaries, evidence of the national economic burden of comorbid T2DM among Medicare beneficiaries with HIV/AIDS would be important to Medicare policy makers as they consider options and ways to address concerns about Medicare's future financial solvency. Also, findings of this study include current

evidence on specific cost domains which are specific for evaluating and generating policies that target a specific aspect of health care use and cost domains. For instance, evidence of total OOP costs and total prescription drug costs would benefit Medicare policy makers as they draft proposals to reduce drug costs, which could be beneficial to HIV positive beneficiaries facing high OOP expenses.

In summary, the significance of this study cannot be over emphasized. It addresses issues that impact both the Medicare system and the patients and their racial identification. The odds of developing T2DM after PIs use and the economic burden of comorbid T2DM provides critical empirical evidence for policy considerations that affects patients and the Medicare.

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